



NATIONAL BLOOD  
AUTHORITY

**ESTIMATING DEMAND FOR FACTOR VIII UP TO 2015**

**A Discussion Paper**



### **NBA Discussion Paper – Estimating Demand for FVIII up to 2015**

Since it commenced operations in July 2003 the National Blood Authority (NBA) has been undertaking research, analysis and national and international benchmarking on the supply, use and cost of all the blood and blood products it is responsible for supplying into the Australian Healthcare System. The NBA does this work to support business activities like the CSL Plasma Products Agreement (PPA) negotiation which the NBA conducted in 2004 and the Defined Blood Products Request for tender (RFT) in 2005-06, and ongoing supply planning and demand forecasting, and to support blood sector reform initiatives from time to time.

The subject of this research paper is forecasting demand for Factor VIII (both plasma-derived Factor VIII and recombinant Factor VIII in Australia). The paper builds on the available data in Australia, mainly the Australian Bleeding disorder Register (ABDR) and NBA data and information. Apart from reinforcing that the critical need for accurate and valid data on Factor VIII use in Australia is still not being fully met, including from the ABDR, this paper makes reasonable assumptions about the missing or incomplete data (for example, patient weight, surgery and product use in tolerisation), and then does demand projections over the next ten years. Interestingly, after adjusting for known differences, on something like prophylaxis, the NBA estimates are relatively close to the ABDR estimates.

The NBA wishes to acknowledge the assistance given by the Australian Haemophilia Centre Directors' Organisation and clinic staff, and by the Australian Bleeding Disorder Register and its staff in the preparation of this Discussion Paper.

The NBA would welcome feedback on this research paper from stakeholders in the Blood Sector in Australia and overseas. Your feedback by end September 2006 would be appreciated.

**Dr Alison Turner, Chief Executive Officer and General Manager**

# National Blood Authority Discussion Paper

## Estimating demand for FVIII up to 2015.<sup>1</sup>

### ***Introduction: the National Blood Authority<sup>2</sup>***

The primary objectives of Australian governments for the Australian blood sector are:

- *to provide an adequate, safe, secure and affordable supply of blood products, blood related products, and blood related services in Australia; and*
- *to promote safe, high quality management and use of blood products, blood related products and blood related services in Australia.*

In pursuing the primary policy objectives, Australian governments have regard to a number of secondary policy aims, including

- *to promote optimal safety and quality in the supply, management and use of products, including through uniform national standards;*
- *to make best use of available resources, and to give financial and performance accountability for the use of resources by all entities involved in the Australian blood sector;*
- *to undertake national information gathering, monitoring of new developments, reporting and research in relation to the Australian blood sector.*

The National Blood Authority (NBA) is an independent statutory agency established under the National Blood Authority Act, 2003 and operating under the National Blood Agreement. It co-ordinates centrally the national planning and purchasing of blood and blood products on behalf of all Australian Governments. Although it is part of the Australian Government Health and Ageing portfolio, the NBA represents the interests of all Australian governments and is jointly funded by all governments on a cost-shared basis. In general State and Territory governments contribute 37 per cent and the Australian government 63 per cent.

The Australian Health Ministers' Conference has ultimate responsibility for management of the sector and the governance, policy and financial arrangements within which the NBA operates. Commonwealth, State and Territory governments are all represented on the Jurisdictional Blood Committee (JBC), a subcommittee of the Australian Health Ministers' Advisory Council. It is the JBC which oversees the NBA and which represents the views of the various jurisdictions on policy, demand, supply planning, product distribution, funding and emerging evidence on new technologies, new products and new services.

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<sup>1</sup> This paper represents a range of estimates prepared by an NBA staff member for discussion. They do not at the moment represent estimates officially accepted by the Authority.

<sup>2</sup> This section draws from the Authority's 2004-05 *Annual Report*, the *National Blood Agreement* and other material available at [www.nba.gov.au](http://www.nba.gov.au).

Under the National Blood Agreement, the NBA has a range of roles and responsibilities which include;

- coordinating demand and supply planning for blood and blood products on behalf of all States and Territories;
- negotiating and managing national contracts with suppliers of blood and blood products;
- working with all governments to ensure that they get the blood and blood products they require, according to an agreed single national pricing schedule;
- supporting policy development and operations within the blood sector through transparent evidence-based processes;
- developing and implementing national strategies to encourage better use of blood and blood products;
- promoting adherence to national safety and quality standards; and
- taking responsibility for national contingency planning.

The execution and timing of the commencement of these activities is governed by the Ministerially approved NBA Corporate Plan, the funding provided by governments, the endorsement of priorities by the Jurisdictional Blood Committee and decisions by the Australian Health Ministers' Council.

With its wide-ranging responsibilities and finite resources, the NBA's priority tasks on its establishment in 2003 were to negotiate and manage supply contracts. It has now been able to turn its attention to other tasks such as facilitating improved clinical use of blood and blood products and providing a national focus on management of blood sector information and data. Its current tasks therefore include:

- continuing to improve contract negotiation and management;
- improving blood and blood product supply management and planning, including contingency planning;
- providing governments an increased capacity to understand and manage expenditure on the blood supply; and
- working with the health sector to improve the quality and appropriateness of blood product use in relation to clinical outcomes.

The NBA, in conjunction with the jurisdictions, plays a critical role in coordinating an annual National Product List and National Supply Plan and Budget for approval by Health Ministers. As part of its role in managing the supply of blood and blood products, the NBA is responsible for:

- collecting data on products issued and reporting to jurisdictions against the approved supply plan;
- making improvements to the national supply planning process;
- monitoring the balance between supply and demand throughout the year; and
- intensively managing products in short supply.

Towards this end, the NBA currently manages ten major agreements with suppliers of blood and blood products valued at around \$650 million in 2006-07.

## ***Demand estimation***

As part of improving its own supply planning, and increasing government capacity to understand and manage blood-related expenditure, the NBA is extending demand estimation further forward than it has hitherto attempted. As demand estimates underpin NBA arrangements with suppliers, the closer our estimates are to actual demand, the greater will be our ability to improve the likelihood of products being available when required by patients. Of course the further out into the future estimates are, the less reliable they become. However, by making its estimates publicly available, the NBA hopes that it will receive comments (from clinicians, researchers, suppliers and stakeholders generally) that will enable the estimates to be as realistic as possible.

## ***Why the interest in Factor VIII at this time?***

Amongst the NBA's many responsibilities is co-ordinating national demand and supply planning of blood and blood products<sup>3</sup> and purchasing these products on behalf of all Australian governments. Blood clotting factors comprise a significant portion of the National Supply Plan and the quantities purchased have increased significantly in recent years. This has not only contributed to the significantly improved quality of life for those people who need the products, but the products can be life saving to those with bleeding disorders. It is therefore critical that we anticipate, understand and plan for future requirements. This is particularly important when production has a long lead time. Furthermore, governments have an expectation that they, through the NBA, are able to understand the reasons for this growth and have confidence in future projections.

Amongst the NBA's many stakeholders are 3,238<sup>4</sup> Australians on the Australian Bleeding Disorder Register (ABDR). These are people being seen/ treated by the Haemophilia Treatment Centres across Australia which contribute to the Register.<sup>5</sup> This group expects government to have a secure supply of the products they need and accurate demand projections are therefore critical to their welfare.

The largest of this group are some 1296 Haemophilia A patients who are deficient in Factor VIII (FVIII), an essential blood clotting factor. The most significant group in terms of product use are the 483 classified as having severe Haemophilia with less than 2% of the normal level of FVIII. The next largest group have von Willebrand's disease, and can also be treated with FVIII, if treatment is required.<sup>6</sup> The third largest group is the 396 people nationally with Haemophilia B, characterised by deficiency of FIX.

Until quite recently, patients with Haemophilia A or B, led a very constrained lifestyle. They were subject to spontaneous bleeds into the joints. They had early joint replacements, they could not participate in most sports, and they had lower than average life span. Their treatment with plasma-derived product was found to have exposed them to infection with HIV and/or Hepatitis C, and many died.<sup>7</sup>

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<sup>3</sup> Ibid

<sup>4</sup> Reported in April 2006 as the number at December 2005.

<sup>5</sup> It does not include overseas visitors, overseas students, and others without permanent residence status. To the extent that they are treated by the Centres (presenting through Emergency) this will distort figures for apparent product use per capita.

<sup>6</sup> Von Willebrand's disease is very common, with up to 1 in 100 affected. Very few require treatment, and if they do it will most usually be by haematologists rather than at Haemophilia Treatment Centres. So not all recognised von Willebrand patients appear on the ABDR.

<sup>7</sup> See Street and Ekert, "Haemophilia – darkest hours before the dawn", Medical Journal of Australia, 1996; 164:453

At the same time as the plasma-derived product was being improved, recombinant FVIII became available for clinical trial (1998) and has been actually used in Australia since 1995. Australian governments have offered all Australian haemophilia patients the choice between recombinant and plasma-derived products. Most have chosen recombinants. Some have not, on clinical advice in particular circumstances<sup>8</sup> or from personal preference.

For Von Willebrand's patients receiving FVIII, it is the plasma- derived product they require. There are 1124 von Willebrand's patients, 62 of them classified as severe. Those who are treated (71 at the most recent count) do not appear to need nearly as much product as patients with severe Haemophilia A, although data is incomplete. We do know that few are regular users of FVIII, and we are told that the amount of product used by the group has not increased in line with increasing numbers. This is in contrast with severe Haemophilia A where average product use per patient more than trebled between 1992 and 2005.<sup>9</sup>

### ***Estimating FVIII demand a decade ahead***

This paper looks at some of the drivers and influences on FVIII demand, makes some assumptions about their possible magnitude, and calculates the possible effects over the next decade if there are:

- no major changes in products and their application;<sup>10</sup>
- no major changes in clinical or surgical practice;
- no changes in government policy with respect to supply and use of FVIII; and
- no changes in government policy with respect to immigration by families with haemophilia or the entry of overseas students with haemophilia.

In what follows, it is assumed that von Willebrand's patients account for 4 million IU of plasma- derived product (pdFVIII) each year. This has been taken out of current demand before estimating increased demand by Haemophilia A patients. The von Willebrand's component is then added back in when calculating demand for pdFVIII and total FVIII for all patients.

### ***Population***

The estimated population of Australia at the end of 2005-06 was 20.5 million. The net increase in population was estimated by the ABS to be 1 person every 2 minutes and 12 seconds<sup>11</sup> or 0.24 million per annum.

During 2005 the Australian Bureau of Statistics believed the rate of population growth would fall after that year. This is not a belief universally held. The immigration rate is probably unlikely to fall, and the birth rate for a number of reasons may be maintained.

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<sup>8</sup> There are, for instance, people undergoing product- intensive tolerisation with plasma- derived FVIII

<sup>9</sup> ABDR Report

<sup>10</sup> One matter to watch, for instance, is whether the development of inhibitors continues to be perceived as a challenge with new- generation recombinant products.

<sup>11</sup> This is based on one birth every 2 minutes and 0 seconds, one death every 3 minutes and 55 seconds, and a net gain of one international migrant every 4 minutes and 47 seconds

However these estimates assume for the moment that the absolute increase in population will remain at the current level which is consistent with the notion of a rate of increase falling slightly and continuously.

With an estimated occurrence of Haemophilia A of up to 1 in 10,000, that means we can expect up to 24 new Haemophilia A patients a year, assuming that the rate of Haemophilia A in the immigrant population is no different from the current residential rate. With Haemophilia A sufferers now enjoying average life expectancy we can assume this is a net increase of 24 annually. Not every one with Haemophilia A may require treatment, and it is the proportion of those 24 who are classified as severe who will have a significant impact on product use.

### ***Prophylaxis***

Between 1992 and 2005, average product use annually for severe haemophilia patients more than trebled. This was in large measure due to increased availability of product for prophylaxis (prevention of spontaneous bleeds) and tolerisation. Substantial increases in product use by the haemophilia community have been observed in other developed countries over the same period. Apparent per capita use is only for broad comparisons. It encompasses varying degrees of severity, varying ages, prophylaxis and on-demand treatment, differing clinical practice, differing government policies and different pricing regimes.

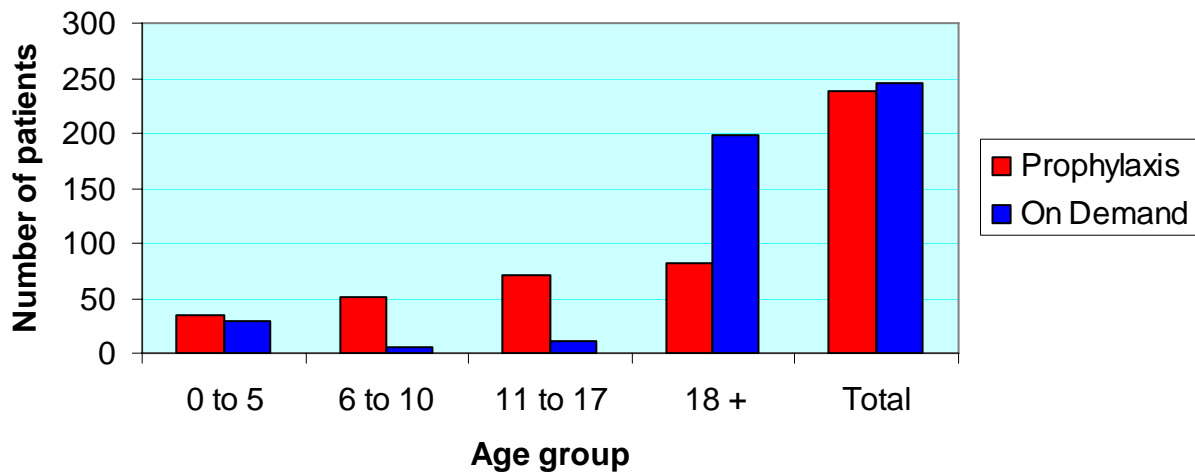
In the past, haemophilia patients were treated from a limited supply of plasma- derived product as their bleeds occurred. There were, as mentioned earlier, severe limitations on lifestyle choices, and early joint damage and surgery. With the introduction of recombinants, and alleviation of the supply restriction of earlier years, prophylaxis (particularly for severe cases) was routinely introduced in childhood (regular treatment, probably 3 doses a week). Sport is possible. Though non-contact sport such as swimming may still be advised, the advice is not always taken. Bleeds are unlikely, and early joint surgery is not necessary. Children's quality of life has improved dramatically.

Many adults expect to continue prophylaxis. Of the 238 Haemophilia A patients receiving prophylaxis at April 2006, 82 (34%) were eighteen or over. Some young men drop out of prophylaxis when they leave home (some because they have never administered the product themselves, some because the treatment no longer fits their lifestyle arrangements.) Some reduce their treatments from three to two a week. The main benefit of prophylaxis for adults, as for children, is seen as improved quality of life and fewer acute hospital admissions.

Some of the 82 adults may opt for hybrid prophylaxis (on-demand/prophylaxis) where they "prime" with FVIII prior to embarking on events such as contact sports or extreme sports that could lead to a bleed.

The following chart illustrates for Australia as a whole the current emphasis on prophylaxis in children. As time passes, older people not on prophylaxis will be replaced by those who have been on prophylaxis all their lives, and expect to continue it.

## Prophylaxis by age groups, patients with severe Haemophilia A, April 2006



This means that increased product use from prophylaxis will continue for some time.

In October 2005, the ABDR prepared a Report for the NBA, *Projection of plasma derived and recombinant FVIII requirements with prophylaxis continued into adulthood*. This could not give a national picture, as NSW was not included in the ABDR for the period from which data was derived. However, it shows for the rest of Australia that, between 2003 and 2004, the number of patients on prophylaxis increased from 142 to 159, and product use for prophylaxis increased by around 12%. By 2004, almost half the severe Haemophilia A patients were on prophylaxis.

By April 2006, with NSW figures added to the register, there were 238 Haemophilia A patients nationally on prophylaxis. This constituted 49% of those registered as “severe”. This proportion is expected to rise continuously over the next decade. With severe Haemophilia A patients currently representing 37% of the national Haemophilia A population, and with prophylaxis extending in both breadth and depth, it may be reasonable to assume 6% as an approximate annual rate of increase in national product use per capita<sup>12</sup> arising from prophylaxis. This could be an underestimate, as treatment practices are still being developed.

### **Body Mass**

Product used is calculated with reference to body mass. Obesity rates in Australia have more than doubled over the past 20 years. Boys with haemophilia used to be inactive because activity was likely to lead to bleeding episodes and joint damage. Prophylaxis in childhood has lessened the need for them to be so cautious, but now their inactivity patterns follow those of other Australian children. The single-event increase in body mass at puberty has a significant impact on product use, so if the cohort in that age group is increasing in number this will affect the estimates.

<sup>12</sup> “per capita” here and in what follows refers to registered Haemophilia A patients at any given time

These estimates use a 0.5% increase annually in per capita product use for increasing body mass. Some allowance for body mass has already been included, via the ABDR prophylaxis estimates above. This assigned average weights from the general population by age to each person. Future adult weights were assigned using averages for adult groups from an ABS survey.

### ***Inhibitors***

The ABDR reported to the NBA in July 2006 on *Issue and Treatment outcomes (Inhibitor) for Patients with Haemophilia*. It demonstrated a lack of information on tolerisation treatment regimens but did conclude that rFVIII is predominantly used. Further work needs to be undertaken here. Meanwhile, as patients with inhibitors were included in the data collection for the October 2005 Report, no separate estimate has been made here.

### ***Surgery***

As Haemophilia A patients can for the most part now expect an average life span, there has been an increase in the surgery of later years – cardio-vascular, orthopaedic, oncology etc. Just how significant this is in terms of product use is not known nationally, and is an area where the ABDR could directly support significant work.

Until this is done, a notional figure must suffice. This estimate uses 5% per annum increase in per capita<sup>13</sup> product use for increased surgery. This may well be a conservative estimate for the next decade, until the new pattern stabilises. However if modern “bloodless surgery” techniques prove to be particularly applicable for haemophilia patients, this could have a major impact on product use. In “bloodless surgery” any blood loss is scavenged and returned.

The 5% assumption does take account of the fact that prophylaxis with FVIII should be reducing surgery for young adults for joint replacements although it uses more FVIII in the process. This was allowed for in a previous section.

### ***Estimates***

The starting points for product use are the NBA’s purchases for 2005-06: 88,155,250 IU recombinant (rFVIII), together with plasma- derived (pdFVIII) purchases of 16,545,500IU. Total annual FVIII use could therefore be said to be 104,700,750 IU.

As mentioned earlier, von Willebrand’s patients have been allocated in this model 4 million IU of pdFVIII. With this initially removed, it is assumed that for Haemophilia A patients pdFVIII continues to represent 15.8% of demand. The projected von Willebrand’s usage is then added back. Table 1 and the chart following show possible demand for FVIII on the assumptions mentioned earlier, in brief:

- constant absolute increase annually in population;
- increase for body mass 0.5% per annum per Haemophilia A patient;
- annual increase through prophylaxis 6% per annum per Haemophilia A patient; and
- annual increase due to surgery 5% per annum per Haemophilia A patient (this could be substantially revised if the ABDR is in future able to provide data on this matter).

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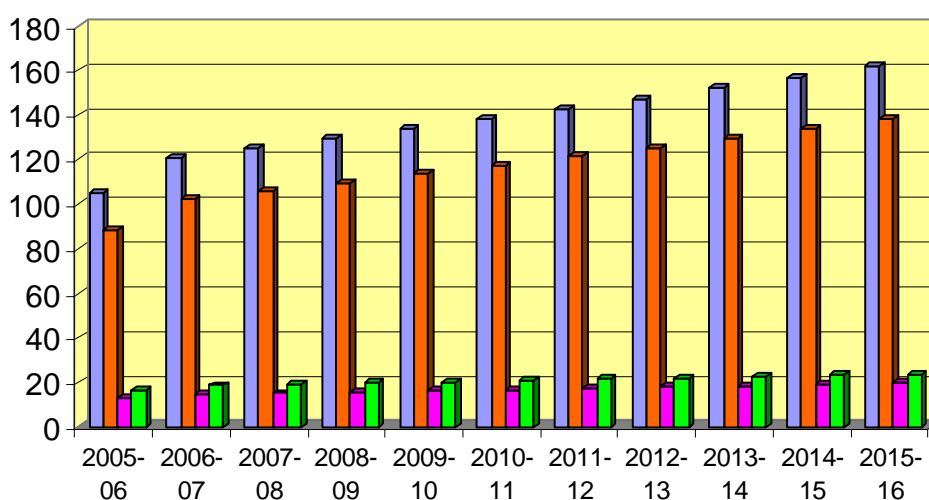
<sup>13</sup> “per capita” refers here to registered Haemophilia A patients

**Table 1: Estimated FVIII demand in mIU, 2005-06 to 2015-16**

	Total FVIII	rFVIII	PdFVIII
2005-06	104,545,500	88,155,500	16,545,500
2006-07	120,478,116	101,967,258	18,510,858
2007-08	124,752,189	105,708,866	19,043,322
2008-09	129,103,272	109,517,891	19,585,381
2009-10	133,531,366	113,394,332	20,137,033
2010-11	138,036,470	117,338,190	20,698,280
2011-12	142,618,584	121,349,464	21,269,120
2012-13	147,277,709	125,428,154	21,849,554
2013-14	152,013,844	129,574,261	22,439,583
2014-15	156,826,989	133,787,784	23,039,205
2015-16	161,717,144	138,068,723	23,648,421

### Estimated FVIII Demand till 2015-16

Million IU



■ total FVIII (HmA and vWF) ■ total rFVIII ■ pdFVIII (HmA) ■ pdFVIII (HmA and vWF)

#### ***The plasma- derived FVIII estimates***

There are a number of reasons why demand estimates for pdFVIII are uncertain, and the proportion of total FVIII demand filled by the plasma derived product could fall rather than continue to grow slowly as shown above. The demand for plasma-derived product has in the last few months been running higher than forecast, but is widely expected to decrease, albeit slowly, as some older patients, accustomed to and preferring the plasma-derived product, are replaced by children for whom the recombinant product is used.

There are some patients who have been undergoing tolerisation with plasma derived product. They have been heavy users, and they are eventually expected to switch to the recombinant products. However, they may be replaced by new patients undergoing

tolerisation. The July 2006 ABDR report on inhibitors (mentioned earlier) suggested rFVIII was being used routinely. There is some suggestion the need for tolerisation may diminish with new recombinant products.

On present indications, people with von Willebrand's disease who use FVIII will need to continue to use the plasma-derived product. However, FVIII is not necessary for the treatment of people with mild or moderate von Willebrand's disease (except for a few patients at the "high" end of the moderate category). Adjunctive agents can be used – DDAVP (Desmopressin), tranexamic acid (antifibrinolytic), fibrin glue and Aprotinin. Even in severe cases, where FVIII may be needed in surgery, it will be supported and extended with the use of these adjunctive agents.

### ***The FVIII estimates overall : reality check***

The October 2005 ABDR estimates concerning prophylaxis, referred to earlier, provide some basis for comparison. That report records the FVIII issues for patients with severe Haemophilia A recorded on the ABDR. Including both prophylaxis and on- demand patients, the ABDR figure for total issues in 2004 was 41,649,089 IU. The NBA figure for the same period was 93,082, 250. So the ABDR study accounted for only 44.7% of total use.

The figures above for total FVIII use in 2013-14 and 2014-15 can be averaged to give a figure for 2014 of 161,717,144 IU. The ABDR October 2005 projections, for 2014, range from 59,028,834 IU to 91,302,682 IU which, if they are grossed up by the factor by which they fell short for 2004 gives a range with a midpoint of 168,005,717. This suggests that the estimates given in this paper are conservative.

To refine these estimates of potential product requirements the NBA needs:

- further advice from the ABDR on prophylaxis (now that NSW figures are available);
- further advice from the ABDR on inhibitors and product use;
- advice on increases due to surgery, including whether or not surgery is going to increase and at what rate; and
- tracking and reporting by the ABDR of the impact of obesity on product use.

While that information about product use is important, the NBA also needs advice on estimating growth in the population with severe Haemophilia A and on the patients being treated. This includes:

- advice from the ABDR, within the limits of privacy requirements, of the source of new registrations on the ABDR in terms of birth versus immigration;
- advice from the ABDR, within the limits of privacy requirements, of the source of deletions from the register in terms of death versus emigration;
- advice from the ABDR on volumes of products being used for patients who are not included in the ABDR eg overseas students and overseas tourists requiring emergency treatment; and
- advice from the ABDR on the amount of product wastage which should be factored into demand estimates.

The NBA already receives information from the ABDR on whether the proportion of the Haemophilia A population classified as severe is changing.

### ***Monitoring demand growth***

The estimates above are just that. The NBA tracks demand to see how it is actually moving at any given time. It will also be watching for factors which may cause significant shifts in demand, for example if

- The population begins to increase at a substantially faster rate than the ABS currently believes. This may be by immigration, including acceptance of refugees.
- The Haemophilia A population increases faster than the growth rate for total population suggests. Australia is a preferred destination for families with haemophilia. This could be offset by a decline in overseas student numbers.
- The obesity epidemic in the population either worsens or begins to abate
- The lifetime pattern of surgery for Haemophilia A stabilises so per capita demand for FVIII for this purpose begins to level out
- The pattern for prophylaxis at all ages stabilises and per capita demand levels out
- Clinical and surgical practices change
- New products become available
- Government policies change

### ***Reader comments are sought***

Demand estimates will always be a mixture of fact and judgment. If you have information or comments that will assist us in the issues discussed in this paper, please email them to [nationalbloodauthority@nba.gov.au](mailto:nationalbloodauthority@nba.gov.au). We are especially interested in your views on the nature and timing of factors with major impact on demand such as the assumptions made above about increased use of recombinant FVIII for surgery and prophylaxis, or through increased body mass. Thank you for your interest.