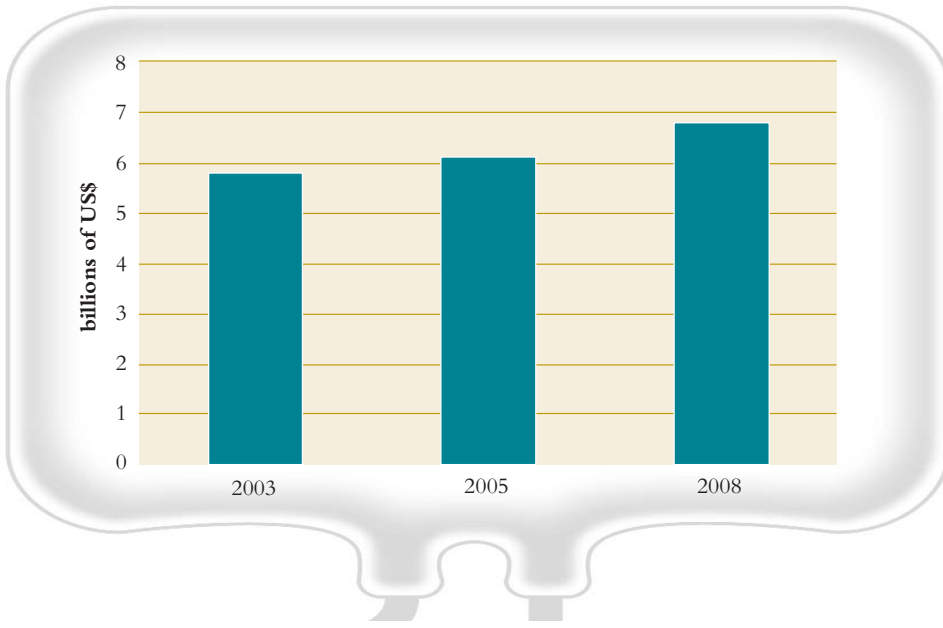
# Chapter 2
## Global demand for plasma products

The global plasma market exceeds US$6.9 billion and is both very dynamic and highly complex. The market overall is driven by the United States and Europe, specifically with respect to intravenous immunoglobulin (IVIg), but China, Brazil and other countries are major drivers for products such as albumin and plasma derived Factor VIII.

The market for plasma products grew by about 5% between 2003 and 2005 and is forecast to increase by a further 11.5% between 2005 and 2008 (fig. 2.1).

Products expected to experience significant growth in the immediate future are IVIg, alpha-1 antitrypsin, fibrin sealants, and minor coagulant products. In March 2006, Mr Jan Bult, President of the Plasma Protein Therapeutics Association, made the following points to the annual International Plasma Protein Congress in Prague: demand for IVIg is growing globally at 3–5% per annum; once-large albumin inventories have been depleted; plasma derived Factor VIII is being used to a greater extent in the treatment of people who have developed inhibitors in response to recombinant products; demand for von Willebrand factor is increasing strongly; and in the past two years in the United States there has been a 25% increase in demand for treatment of people with emphysema and alpha-1 antitrypsin deficiency.[1]

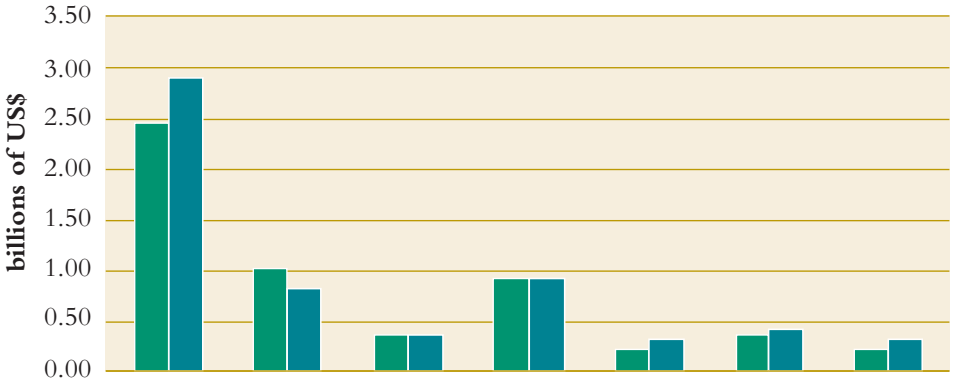
**Fig. 2.1** Projection of global sales of plasma products




Source: Derived from Marketing Research Bureau data, and from data in Baxter Healthcare Pty Ltd submission to Plasma Fractionation Review, 2006.

1 Jan Bult, 'Market and Industry Developments', paper presented to the International Plasma Protein Congress, Prague, 7–8 March 2006.

**Fig. 2.2** Global demand for plasma derived products, 2005 and 2008




| | IVIg | pdFVIII | pdFIX | albumin | anti-inhibitor | fibrin | alpha-1 |
|---|---|---|---|---|---|---|---|
| 2005 | 2.45 | 1.00 | 0.35 | 0.90 | 0.20 | 0.35 | 0.20 |
| 2008 | 2.90 | 0.80 | 0.35 | 0.90 | 0.30 | 0.40 | 0.30 |

Source: Derived from Marketing Research Bureau data, 2005.

Research undertaken by consultants engaged for the Review indicates that albumin sales are forecast to remain static in the period 2005–08, while sales of plasma derived Factor VIII and Factor IX will decline in favour of sales of recombinant alternatives (fig. 2.2).

IVIg has been for some time the high-growth product within the plasma derived product sector, at both a global and an individual country level.

At the global level, this trend continues for IVIg because other contenders (i.e. albumin and clotting factors) have been subject to marketplace changes that have limited their expansion. In the case of albumin, there has been debate about the relative merits of this product when compared with alternatives such as normal saline. Only after the publication in 2004 of scientific evidence that reaffirmed albumin's value as a therapeutic agent in trauma care, have sales begun to recover.[2] China in particular is importing increasing quantities of albumin.

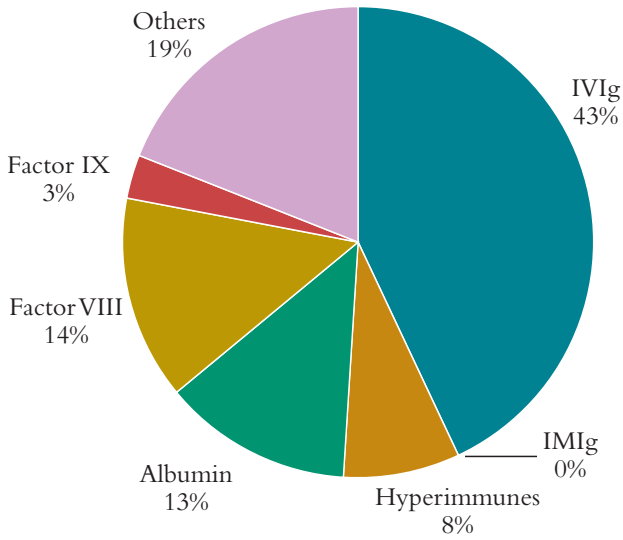
In the area of clotting factors, recombinant technology has diminished the potential for plasma derived products to lead global market growth. There seems little prospect, however, that a recombinant IVIg will be available in the foreseeable future to challenge the market leadership position of plasma derived IVIg.

Figure 2.3 shows the estimated shares of the global market held by the various plasma products in 2005–06.



2 S. Finfer, R. Bellomo, N. Boyce, J. French, J. Myburgh & R. Norton [The SAFE Study Investigators], 'A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit', *New England Journal of Medicine*, vol. 350, no. 22, 27 May 2004, pp. 2247–56. This study is widely referred to as the SAFE Report.

**Fig. 2.3** Global plasma products market, by product share (US$6.933 bn)




Source: Adapted from Marketing Research Bureau data supplied October 2006.

The demand for and supply of plasma derived products is closely bound up with global fractionation capacity, which is influenced not only by demand and supply factors, but also by the economic and regulatory environment.

In the late 1990s and early 2000s, the fractionation industry in the United States was subjected to a number of regulatory interventions, leading to the temporary closure of some plants. The resulting downturn in product supply led directly to price inflation, followed by a period of reinvestment undertaken with a view to increasing production.

This series of factors culminated in over-capacity and a downward price spiral, compounded by the increasing market impact of recombinant products (see Chapter 3).

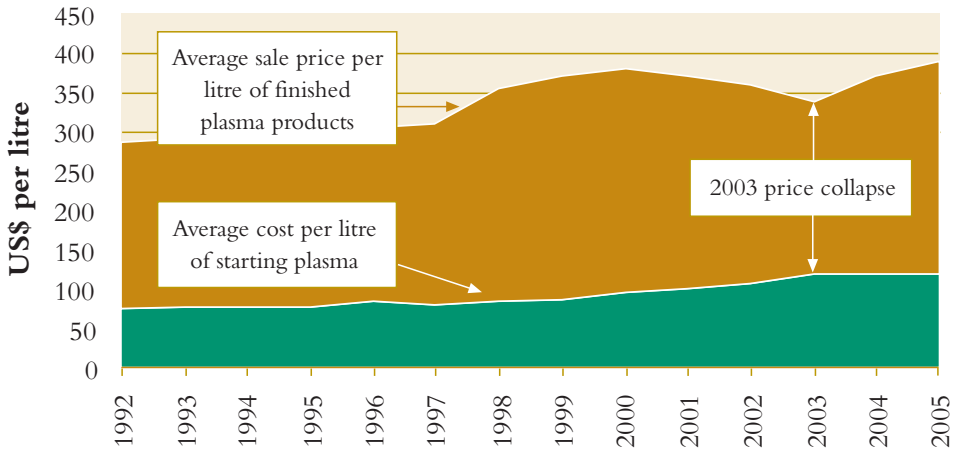
By 2004, the US market had come back into balance, with this shift leading to steadily increasing prices and renewed demand pressures.

Figure 2.4 shows the impact of these various events upon the average global cost per litre of starting plasma and, more significantly, upon the variation in the average global price per litre of finished plasma products.

The fluctuations in the world's largest market caused flow-on effects globally, opening the way for a series of rationalisations and takeovers. The result has been a global industry that is fundamentally different from the industry as it existed in earlier periods.

The effects of these various events can be seen in figures 2.5–2.8, which map historical volumes and trend projections for individual plasma products.

**Fig. 2.4** Starting plasma cost per litre and sales per litre




Source: Derived from data in: Jan Bult, 'Market and Industry Developments', paper presented to the International Plasma Protein Congress, Prague, 7–8 March 2006.

## Projected demand for principal plasma products

### Intravenous immunoglobulin (IVIg)

A projected trend out to the year 2016, with respect to the global demand for intravenous immunoglobulin, is set out in figure 2.5. The trend is based on historical demand figures dating from 2000 onwards and suggests an increase in demand of 5.1 tonnes annually for the period 2006–16.

The projected trend takes account only of factors that are already embedded in the historical figures. The use of IVIg for new indications, changes in clinical practice, or the expansion of use into new markets, could generate demand beyond the levels projected here. It is important to note that there is no international consensus on expected growth rates for IVIg.[3]

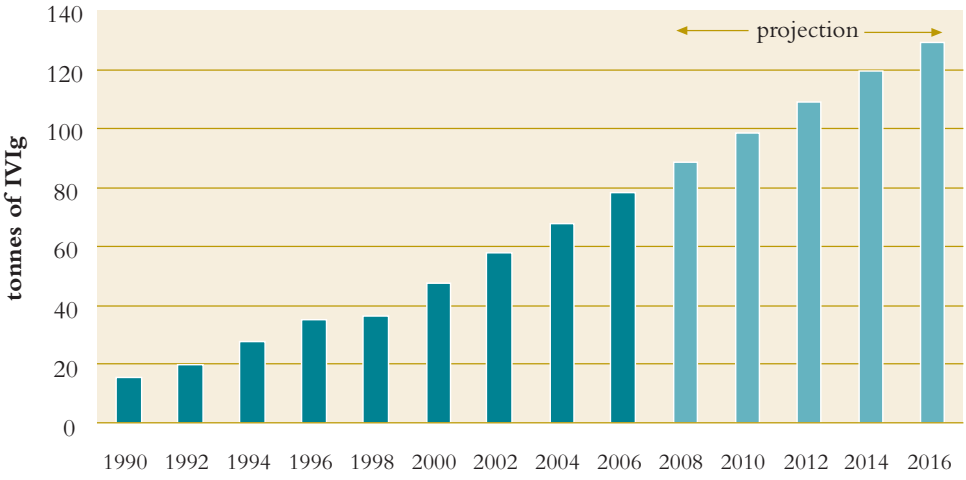
As table 2.1 indicates, rates of IVIg consumption across the various markets are by no means uniform.

The reasons for the substantial differences in consumption rates between countries are not clear, but relate to differences in clinical practice, the presence or absence of price signals at prescriber level, and/or funding levels for health services.



3 See National Blood Authority, *The Supply and Use of Plasma Products in Australia*, National Blood Authority, Canberra, 2006, p. 25; also available online at <http://www.nba.gov.au/pubs.htm>.

**Fig. 2.5** Intravenous immunoglobulin (IVIg) actual global consumption and projection




Source: Derived from data in: Patrick Robert, 'Market Statistics and Trends', paper presented to the International Plasma Protein Congress, Prague, 7–8 March 2006.

**Table 2.1** International usage rates for IVIg, 2005

| Country/province | Usage rate (g/1000 population) |
|---|---|
| Quebec | 126 |
| United States | 105 |
| Canada | 92 |
| Sweden | 81 |
| Australia | 73 |
| Austria | 67 |
| Belgium | 67 |
| France | 47 |
| New Zealand | 46 |
| Italy | 40 |
| United Kingdom | 39 |
| Germany | 38 |
| Netherlands | 35 |
| Japan | 28 |
| China | 3 |

Source: National Blood Authority, *The Supply and Use of Plasma Products in Australia*, National Blood Authority, Canberra, 2006, p. 24; also available online at <http://www.nba.gov.au/pubs.htm>.

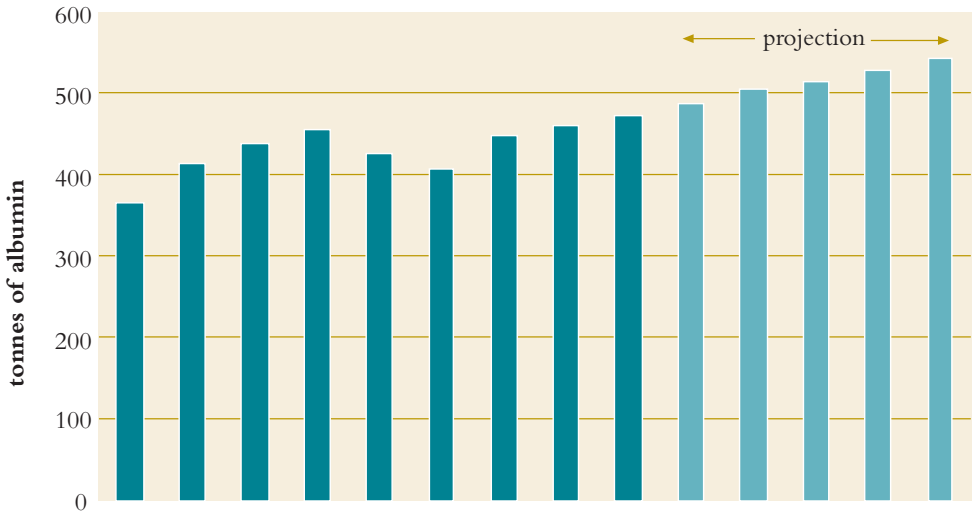
## Albumin

The use of albumin globally has in recent years been significantly influenced by two reports. The Cochrane Report, published in 1998, suggested that the product may be associated with higher levels of mortality when compared with alternatives such as glucose or saline.[4] This finding caused a material decline in albumin usage. The publication in 2004 of the SAFE Report, which concluded that albumin was as safe as alternatives and could be used with confidence,[5] stimulated a recovery in albumin sales.

Figure 2.6 shows that the level of demand for albumin has not been increasing at the same rate post-2004. In the development of the forward trend projection, all figures prior to those for 2004 have been excluded, so as to remove the effects of the demand decline and subsequent recovery.

It is possible that the global demand trend for albumin will become steeper as developed and developing countries increase clinical usage. As noted earlier, China, in particular, is importing increasing quantities of albumin.

**Fig. 2.6** Albumin actual global consumption and projection




| | 1990 | 1992 | 1994 | 1996 | 1998 | 2000 | 2002 | 2004 | 2006 | 2008 | 2010 | 2012 | 2014 | 2016 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| tonnes of albumin | 365.6 | 414.4 | 439.6 | 455.7 | 427 | 405.8 | 447.9 | 460.4 | 474.3 | 488.2 | 502.1 | 516 | 529.9 | 543.8 |

Source: Derived from data in: Patrick Robert, 'Market Statistics and Trends', paper presented to the International Plasma Protein Congress, Prague, 7–8 March 2006.

4 Cochrane Injuries Group Albumin Reviewers, 'Human Albumin Administration in Critically Ill Patients: Systematic Review of Randomised Controlled Trials', *British Medical Journal*, vol. 317, no. 7153, 25 July 1998, pp. 235–40.

5 See note 2 above.

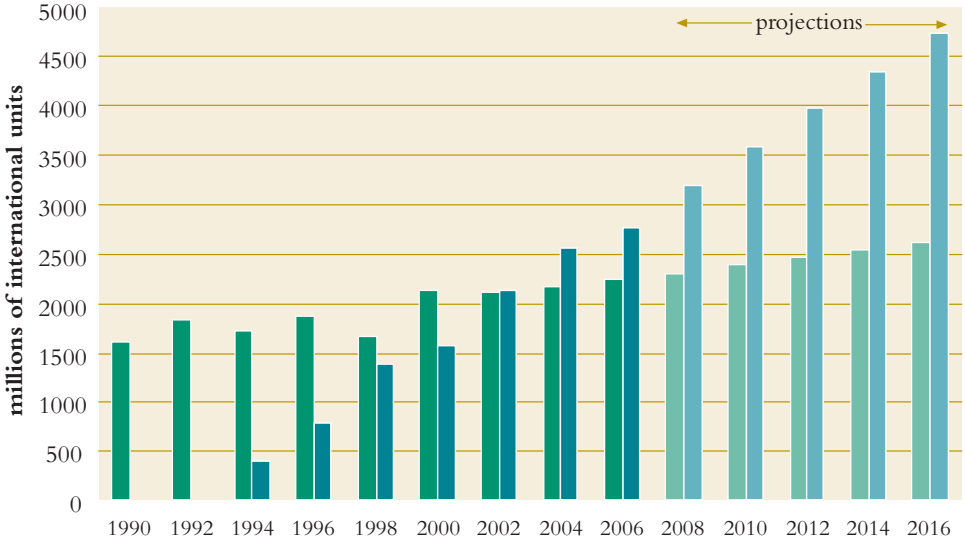
## Factor VIII

From the late 1960s to the mid 1990s, plasma derived Factor VIII was the driving product for plasma fractionators. In the early 1990s, however, recombinant forms of the product started to become available in developed markets. The market dynamics that ensued are indicated in figure 2.7.

Contrary to some expectations, demand for plasma derived Factor VIII has continued to grow (albeit at a slower rate than the recombinant form). There are a number of factors at work, including different countries' varying rates of conversion from plasma derived to recombinant products, differing clinical practices and preferences, and the emergence of immune tolerance and inhibitor issues for some patients treated with the recombinant form.

The trend projection for plasma derived Factor VIII shows an annual growth expectation of approximately 75 million units per year from 2008 onwards. At the same time, the demand for the recombinant form is projected to increase by approximately 400 million units annually from 2008.

**Fig. 2.7** Plasma derived and recombinant Factor VIII actual global consumption and projections




| | 1990 | 1992 | 1994 | 1996 | 1998 | 2000 | 2002 | 2004 | 2006 | 2008 | 2010 | 2012 | 2014 | 2016 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| pdFVIII IU. mill | 1612 | 1837 | 1719 | 1878 | 1663 | 2124 | 2111 | 2174 | 2240 | 2308 | 2384 | 2460 | 2536 | 2612 |
| rFVIII IU. mill | 0 | 0 | 410 | 786 | 1375 | 1581 | 2115 | 2566 | 2767 | 3203 | 3586 | 3969 | 4352 | 4735 |

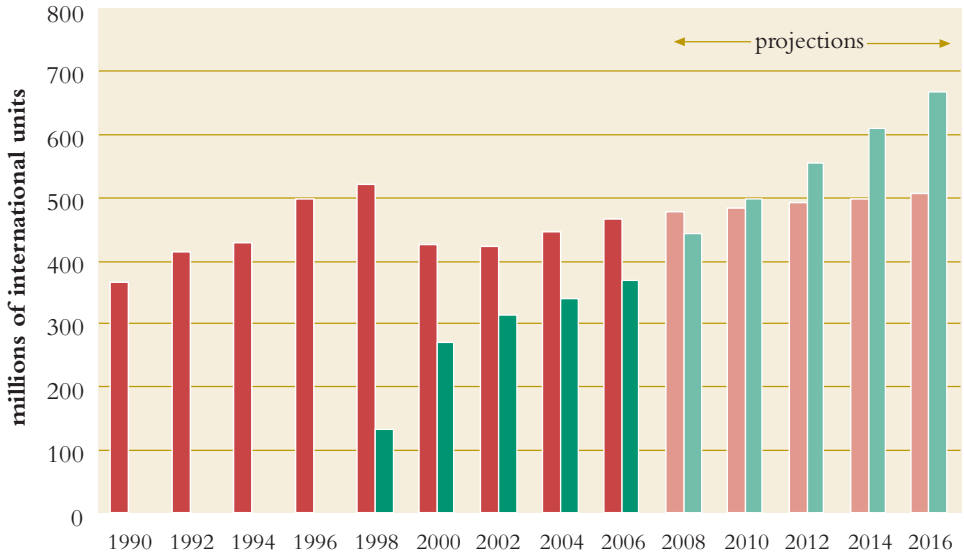
Source: Derived from data in: Patrick Robert, 'Market Statistics and Trends', paper presented to the International Plasma Protein Congress, Prague, 7–8 March 2006.

## Factor IX

By 2002, demand for recombinant Factor IX had similarities with that for recombinant Factor VIII. The patterns of subsequent change, however, as seen in figure 2.8, are quite different.

The introduction of recombinant Factor IX followed the introduction of recombinant Factor VIII by approximately four years. It is not expected that demand for the recombinant form of Factor IX will exceed that for the plasma derived form until 2010. However, while demand for plasma derived Factor IX is expected to increase marginally, by approximately 7 million units per year, from 2008 onwards, demand for the recombinant analogue is likely to increase by approximately 57 million units annually from 2008.

**Fig. 2.8** **Plasma derived and recombinant Factor IX actual global consumption and projections**




| | 1990 | 1992 | 1994 | 1996 | 1998 | 2000 | 2002 | 2004 | 2006 | 2008 | 2010 | 2012 | 2014 | 2016 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| pdFIX IU. mill | 365 | 415 | 428 | 498 | 520 | 426 | 424 | 445 | 467 | 478 | 485 | 492 | 499 | 506 |
| rFIX IU. mill | 0 | 0 | 0 | 0 | 133 | 272 | 315 | 340 | 368 | 442 | 498 | 555 | 611 | 668 |

Source: Derived from data in: Patrick Robert, 'Market Statistics and Trends', paper presented to the International Plasma Protein Congress, Prague, 7–8 March 2006.

## Demand for other plasma derived products

### Intramuscular (normal) immunoglobulin (IMIg)

Global use of intramuscular immunoglobulin (IMIg) has been affected by the advent of hepatitis A vaccines. The future demand for IMIg is uncertain, because of emerging factors such as the increased propensity, given its suitability for self-administration, to use this immunoglobulin as an alternative to IVIg (a positive factor); the increasing use of subcutaneous immunoglobulin (SCIg), instead of IMIg, in self-administration regimes (a negative factor); and the increasing use of hepatitis A vaccines (a negative factor).

### Hyperimmune immunoglobulins

Hyperimmune immunoglobulins are highly specialised products for use in the control of specific infectious diseases and in the treatment of, and prophylaxis with regard to, anti-D in pregnancy. Apart from demand for Rh(D) immunoglobulin, the global requirement for hyperimmunes is at a comparatively low level, as the incidence of diseases such as tetanus and cytomegalovirus infection has become less pronounced in developed countries. Relatively few manufacturers are involved in the production of these low-volume, high-value products, which depend on the collection of starting plasma from small cohorts of donors with specific antibody profiles.

### Factor XI, Factor XIII and Factor Eight Inhibitor Bypass Agent (FEIBA)

Factor XI, Factor XIII and Factor Eight Inhibitor Bypass Agent (FEIBA) are used to treat relatively rare bleeding disorders. The small global demand is met by the few manufacturers, predominantly not-for-profit fractionators, that produce Factor XI and Factor XIII, and by the one commercial fractionator that produces FEIBA.

### Alpha-1 antitrypsin

Alpha-1 antitrypsin is a relatively new product of plasma fractionation and is being used increasingly to treat chronic respiratory disease. Demand is presently concentrated in the United States. It is expected, however, that demand will spread, and that usage levels will increase in future years.

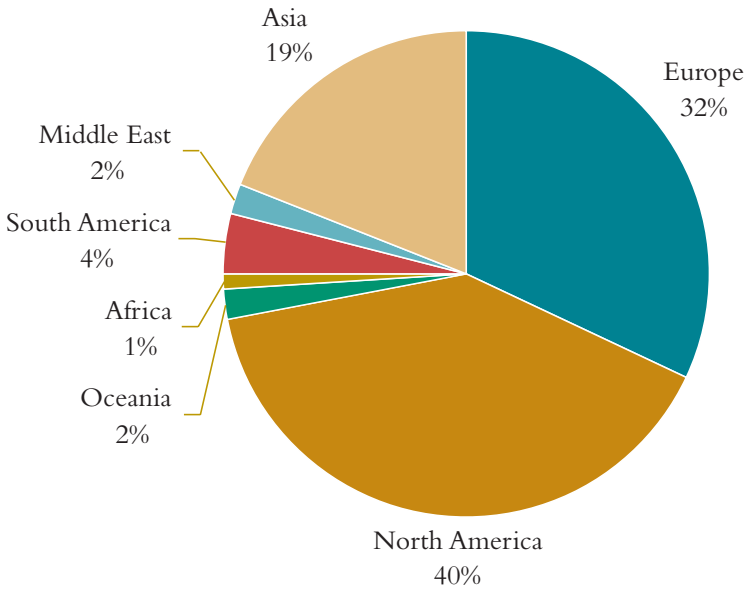
### Fibrin sealants

Demand for fibrin sealants, which are used in place of suturing to seal surgical and other wounds, is largely concentrated in the United States.

## Demand by region

The demand for plasma derived products (and indeed for recombinant alternatives) is centred on North America and Europe. Figure 2.9, a diagram developed from Marketing Research Bureau data, shows the shares of the total global market accorded to each of seven regions, on the basis of the value of product acquired.

**Fig. 2.9** Global plasma products market, by region (US$6.933 bn)




Source: Derived from Marketing Research Bureau data supplied October 2006.

## Global supply

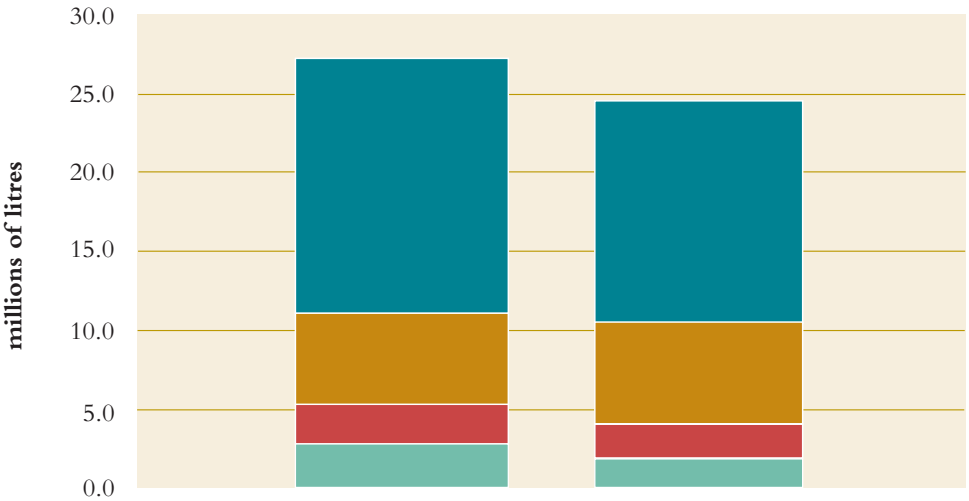
In 2004, the commercial plasma fractionation sector processed 20.5 million litres of plasma, comprising 14.2 million litres of source plasma and 6.3 million litres of recovered plasma. In 2002, the quantities were: 21.8 million litres in total, and 16.0 million litres and 5.8 million litres respectively for source and recovered plasma.

The not-for-profit sector fractionated 4.0 million litres of plasma, comprising 2.1 million litres of source plasma and 1.9 million litres of recovered plasma, in 2004. The figures for 2002 were: 5.4 million litres in total, and 2.6 million litres and 2.8 million litres for source and recovered plasma respectively (fig. 2.10).

The decline in throughput shown here for the period 2002–04 is consistent with the industry rationalisation discussed earlier. Given these circumstances, the question must arise as to how demand for IVIg (which draws on 100% of all fractionated plasma) was met over this period, when there was a reduced throughput of starting plasma. The answer is that steadily improving yields were being achieved, as a result of less wastage, increased batch sizes, and technological improvements in the area of processing. These three factors have contributed to a leaner, more efficient, global industry, which is producing more IVIg from less plasma.

The average capacity of individual fractionation plants worldwide has increased in recent years as a consequence of industry consolidation. Table 2.2 illustrates this point.

**Fig. 2.10** Volume of plasma fractionated by commercial and not-for-profit sectors, 2002 and 2004




| | 2002 | 2004 |
|---|---|---|
| commercial source plasma | 16.0 | 14.2 |
| commercial recovered plasma | 5.8 | 6.3 |
| not-for-profit source plasma | 2.6 | 2.1 |
| not-for-profit recovered plasma | 2.8 | 1.9 |

Source: Derived from data in: Marketing Research Bureau, *International Directory of Plasma Fractionators 2005*, Marketing Research Bureau, Orange, CT, 2005, p. 9.

**Table 2.2** Average capacity of plasma fractionation plants, 1987 and 2005

| Region | Average plant capacity 1987 – '000 litres | Average plant capacity 2005 – '000 litres |
|---|---|---|
| Europe | 162 | 500 |
| North America | 570 | 1144 |
| Rest of world | 116 | 333 |
| **Global average** | **192** | **475** |

Source: Marketing Research Bureau, *International Directory of Plasma Fractionators 2005*, p. 8.

Table 2.3 provides recent figures for the distribution of worldwide fractionation capacity, by region.

**Table 2.3** Worldwide fractionation capacity, by region, 2005

| Region | Total volume in millions of litres | % share of global capacity |
|---|---|---|
| Europe | 14.0 | 41 |
| North America | 10.3 | 31 |
| Asia | 7.3 | 22 |
| **Rest of world** | **2.1** | **6** |

Source: Marketing Research Bureau, *International Directory of Plasma Fractionators 2005*, p. 8.

During the period 1987 to 2004, as a consequence of industry rationalisation, fractionation capacity steadily moved from the not-for-profit sector to the commercial sector, as shown in table 2.4.

**Table 2.4** Relative fractionation capacity of commercial and not-for-profit sectors, 1987, 2002 and 2004

| Status | 1987 | 2002 | 2004 |
|---|---|---|---|
| Commercial | 68% | 75% | 81% |
| Not-for-profit | 32% | 25% | 19% |

Source: Marketing Research Bureau, *International Directory of Plasma Fractionators 2005*, p. 9.

Global production capacity is now largely concentrated in six companies, which together account for 63% of world capacity (fig. 2.11).[6]

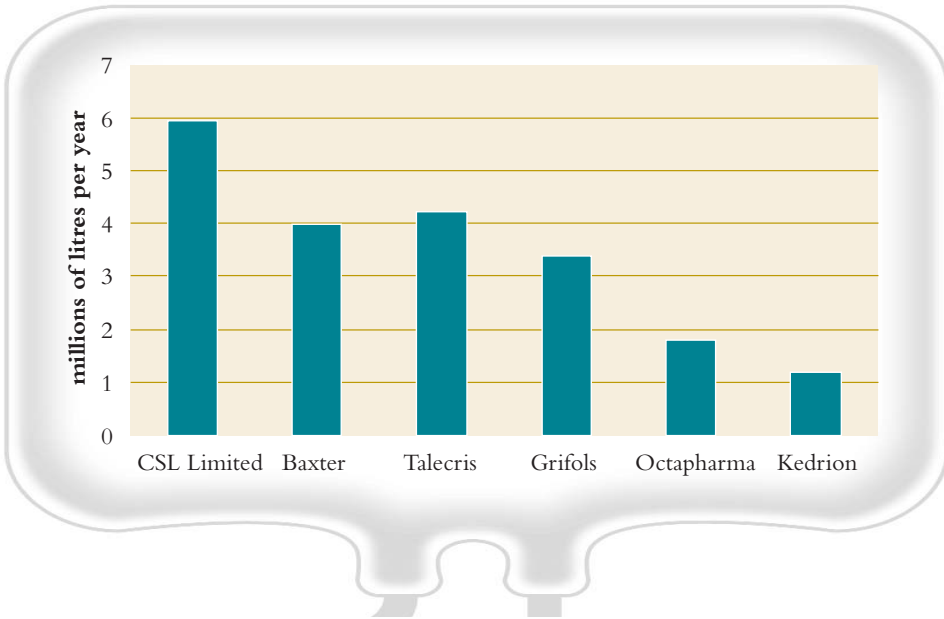
In conjunction with shifts in market demand, there have also been significant shifts in the numbers of fractionators producing individual products. Products less attractive in commercial terms are being phased out and replaced by products with a more secure commercial future (table 2.5).

Table 2.6 identifies the amounts of starting plasma required for the production of varying amounts of IVIg, given different rates of fractionation yield. If requirements with respect to the quantities of raw plasma necessary for the manufacture of IVIg can be met, then most other plasma derived products will be adequately resourced in terms of starting plasma (with the exception of hyperimmunes, which require specialised pools of starting plasma).



6 See Marketing Research Bureau, *International Directory of Plasma Fractionators 2005*, Marketing Research Bureau, Orange, CT, 2005, p. 10.

**Fig. 2.11** Capacity of major fractionators




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

**Table 2.5** Numbers of plants producing various plasma products, 2002 and 2005

| Plasma derived product | Number of plants producing in 2002 | Number of plants producing in 2005 |
|---|---|---|
| Albumin | 73 | 66 |
| IVIg | 43 | 47 |
| IMIg | 32 | 38 |
| Hyperimmunes | 36 | 36 |
| Factor VIII | 38 | 34 |
| Factor IX | 29 | 28 |
| Antithrombin III | 12 | 14 |
| Fibrin sealants | 0 | 10 |
| Other products | 31 | 22 |

Source: Derived from data in: Marketing Research Bureau, *International Directory of Plasma Fractionators 2005*, p. 11.

By applying the global trend projection for IVIg consumption, as provided at figure 2.5, to the data in this table, it is possible to calculate an approximation of the amount of raw plasma that would be required, going forward, for each of the four rates of yield (table 2.7).

**Table 2.6** Levels of starting plasma required for production of various quantities of IVIg

| Input of starting plasma in litres x 1000 (tonnes) → | 300 | 500 | 700 | 900 | 1100 |
|---|---|---|---|---|---|
| Rate of IVIg yield per litre ↓ | IVIg yield in tonnes ↓ | IVIg yield in tonnes ↓ | IVIg yield in tonnes ↓ | IVIg yield in tonnes ↓ | IVIg yield in tonnes ↓ |
| 4.0 g/L | 1.2 | 2 | 2.8 | 3.6 | 4.4 |
| 4.5 g/L | 1.35 | 2.25 | 3.15 | 4.05 | 4.95 |
| 5.0 g/L | 1.5 | 2.5 | 3.5 | 4.5 | 5.5 |
| 5.5 g/L | 1.65 | 2.75 | 3.85 | 4.95 | 6.05 |

Source: Secretariat calculations.

**Table 2.7** Actual and projected demand for IVIg, varying according to rate of yield, 2000–16

| Year | Global demand for IVIg (actual and estimated) in tonnes | Plasma supply requirement in litres x 1000 at 4.0 g/L yield | Plasma supply requirement in litres x 1000 at 4.5 g/L yield | Plasma supply requirement in litres x 1000 at 5.0 g/L yield | Plasma supply requirement in litres x 1000 at 5.5 g/L yield |
|---|---|---|---|---|---|
| 2000 | 47.4 | 11 850 | 10 533 | 9 840 | 8 618 |
| 2002 | 58.2 | 14 550 | 12 933 | 11 640 | 10 582 |
| 2004 | 68.0 | 17 000 | 15 111 | 13 600 | 12 364 |
| 2006 | 78.2 | 19 550 | 17 378 | 15 640 | 14 218 |
| 2008 | 88.5 | 22 125 | 19 667 | 17 700 | 16 091 |
| 2010 | 98.7 | 24 675 | 21 933 | 19 740 | 17 945 |
| 2012 | 108.9 | 27 225 | 24 200 | 21 780 | 19 800 |
| 2014 | 119.2 | 29 800 | 26 489 | 23 840 | 21 673 |
| 2016 | 129.4 | 32 350 | 28 756 | 25 880 | 23 527 |

Source: Secretariat calculations.

These figures demonstrate the importance of yield in circumstances where IVIg demand is increasing at rates that are challenging the ability of the global plasma collection system to provide sufficient starting plasma.

The amount of starting plasma available at a global level is a function of collection practices in individual countries, and these vary considerably. Collection rates are influenced by a range of factors, including population size and levels of growth, demographics, collection methods employed (e.g. plasmapheresis), cultural considerations, the remuneration or non-remuneration of donors, and whether collecting agencies are commercial or not-for-profit.