

# Chapter 3

## The world fractionation industry

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The combined global market for plasma derived products and recombinant clotting factor alternatives is valued at US\$10.5 billion. The market segment for plasma derivatives is estimated at US\$6.9 billion, and the segment for recombinant blood products at US\$3.6 billion.<sup>1</sup> Intravenous immunoglobulin (IVIg) accounts for over 40% of worldwide demand for plasma products.

The global plasma fractionation industry has grown over the past 40 years into a multi-billion-dollar sector. The global industry consists of a small number of high-capacity commercial fractionators with extensive multinational operations, and a large number of medium to small fractionators, which have lower outputs and exist primarily to serve national markets. Aside from the growth in the scale of the industry, there has been an increasing sophistication in the processes that ensure the safety and quality of products; a greater use of chromatography in fractionation technologies; a concentration of the industry into fewer hands; and shifts in the patterns of clinical usage for the various plasma-fractionated products.

The key drivers of demand for fractionation services have also changed over time as new plasma products have become commercially available and new indications for the use of plasma products have been identified and adopted.

Originally albumin was the leading plasma product but its market position changed from the late 1960s onwards, when concentrated Factor VIII became widely available for the treatment of people with haemophilia A. As noted above, IVIg has now emerged as the driving product, as a result of new clinical uses being explored and wider usage following.

The plasma products market in the United States is the largest in the world, and developments there significantly influence the global market. In the mid 1990s, there was quite a different landscape in the US plasma products industry, when compared with that of today. The range of products was also quite different, as recombinant products were yet to achieve dominance in the market for clotting factors: Recombinate® (recombinant Factor VIII), produced by Baxter, was licensed by the FDA in 1992, and Benefix® (recombinant Factor IX), produced by Wyeth, was licensed in 1997.

### Global capacity and production

Global plasma fractionation capacity in 2005 was estimated to be 33.7 million litres per annum, down by 1.5 million litres from 2002. The number of fractionation plants worldwide fell from 80 to 71 between 2002 and 2005. The average capacity of individual plants, however, rose in response to industry concentration. For example, average plant capacity in North America now stands at a little over 1.1 million litres, up from 570 000 litres in 1987 (see Chapter 2, table 2.2).

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<sup>1</sup> Marketing Research Bureau data supplied October 2006.

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The commercial fractionation sector is over four times the size of the not-for-profit sector. The commercial sector provides 27.3 million litres capacity (81% of the global total), while the not-for-profit fractionators provide 6.4 million litres capacity (19% of total capacity) (see Chapter 2, table 2.4). Over the last 20 years the commercial proportion of the industry has been increasing. Between 2002 and 2005 the total capacity of the commercial sector increased marginally (by 0.5%), while that of the not-for-profit sector fell substantially (by 24.3%).

In considering capacity, it is important to note that the throughput of a fractionation plant will vary, depending on the products being manufactured and the technologies employed. In broad terms, it is accepted that chromatography is capable of producing higher yields and greater purity of product than is Cohn technology, and therefore there is an increasing use of chromatographic finishing steps in production cycles based on Cohn primary extraction. Throughput at a large-capacity plant may be optimised where there is specialisation in a particular product or group of products (e.g. IVIg or clotting factors). It is not possible, however, to estimate total theoretical plant capacities, as it is not feasible to make accurate provision for the impact of regular plant maintenance shutdowns.

Some increase in global capacity is forecast through to 2008, when, it is estimated, total theoretical capacity will be 35 million litres, with 30 million litres of plasma actually being processed, giving a capacity utilisation rate of 85%. While according to this scenario the percentage of total unused global capacity is going to fall, there will still be some 5 million litres of theoretical capacity remaining in 2008.

Between 2002 and 2005 the quantity of plasma being fractionated globally fell by 9.9%, from 27.2 million litres to 24.5 million litres. The volume of source plasma fractionated globally fell from 18.6 million litres to 16.3 million litres (representing a 12.5% reduction in the volume of the plasma starting pool). The amount of recovered plasma fractionated worldwide fell from 8.6 million litres to 8.2 million litres (a 4.4% reduction). As noted above, global plasma fractionation capacity for 2005 was an estimated 33.7 million litres, meaning that fractionators had an estimated 9 million litres of unused processing capacity in that year. The reduction in plant throughput was to some extent offset, however, by lower production losses, resulting from improved yields and the processing of larger batches of starting plasma.

Table 3.1 provides a view of the world's leading plasma fractionators, their total theoretical capacities, their total throughputs in 2005, and the capacity utilisation rates achieved. (Global fractionators are profiled more extensively in Annex D.)

### Industry consolidation

In the last ten years a number of pressures on the plasma fractionation industry have led to plant closures, a phase of mergers, takeovers and product acquisitions, and concerted efforts by firms to rationalise operations. The capital intensity of the industry, arising from high infrastructure costs and fixed manufacturing costs, together with the financial exposure of fractionators to the vagaries of supply and demand, are key factors that have driven consolidation and change.

**Table 3.1** World's largest plasma fractionators, by annual capacity, 2005

Fractionator	Headquarters	Capacity - '000 litres	2005 Production - '000 litres	Utilisation (%)
CSL Limited	Australia	5950	5050	84.9
Talecris	United States	4100	2710	66.1
Baxter	United States	4000	3400	85.0
Grifols	Spain	3400	1768	52.0
Octapharma	Switzerland	1800	1600	88.9
Kedrion	Italy	1200	1050	87.5
Chengdu Inst.	China	800	350	43.8
Japan Red Cross*	Japan	800	525	65.6
LFB*	France	800	650	81.3
Shanghai Blood Inst.*	China	800	600	75.0
BPL*	United Kingdom	750	400	53.3
Sanquin*†	Netherlands	800	425	53.1

Source: Derived from Marketing Research Bureau data, 2006.

\* Not-for-profit.

† If the proposed joint initiative between Sanquin and Biotest proceeds, the resultant entity would have a capacity of around 1 million litres, ranking it seventh on the list, by capacity (after Kedrion).

In the late 1990s in the United States, a series of events brought about by temporary plant closures, following FDA intervention, resulted in extensive rationalisation in both the US domestic fractionation industry and the global industry. In 1997, in the wake of a recall of Centeon's albumin product, the FDA required the temporary closure of the plant then owned by Centeon at Kankakee, Illinois (this plant is now owned by CSL Limited). In 1999 the Alpha Therapeutic Corporation plant in Los Angeles (now owned by Grifols) was temporarily closed. The shortages that resulted from these disruptions, particularly in respect of IVIg supply, brought about higher prices in the open US market, spurring commercial fractionators to increase plasma collections as well as output of finished products.

Between 2000 and 2003, however, once the Kankakee and Los Angeles plants had recommenced production, there was an oversupply of products, which led to dramatic price falls and, in turn, to a 30% reduction in gross operating margins. Due to fixed costs representing a high proportion of the total costs of fractionation, this translated into a significant net profit downturn for the industry, resulting in another round of rationalisation.

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Falls in revenue coincided with declining demand both for plasma derived clotting factors (in favour of recombinant products) and for albumin (due to existing perceptions, subsequently discounted, regarding the relative safety and efficacy of albumin when compared with alternative therapies).<sup>2</sup>

One estimate has the net revenue per litre of plasma products (with the cost of plasma collection excluded from the analysis) dropping from an all-time high of about US\$220 per litre in 1999 to just over US\$100 per litre in 2003.<sup>3</sup>

In addition to being exposed to financial impacts attributable to market dynamics, manufacturers in the United States have been required, as a result of increased FDA scrutiny, to:

- spend approximately US\$1 billion, over and above normal maintenance costs, to upgrade facilities so as to meet new regulatory requirements
- expand quality control and quality assurance functions
- phase out low-purity products and abandon development programs for products that would not have met new viral-inactivation standards.

These three factors contributed to the diminished revenue per litre of product, and increased operating expenses and capital expenditure, resulting in a higher break-even volume for individual facilities.<sup>4</sup>

Industry rationalisation has changed the global corporate picture. CSL Limited, having previously acquired the Swiss Red Cross fractionator, ZLB, in July 2000 and 47 US plasma collection centres (out of 56) from Nabi in July 2001, purchased the plasma products business of Aventis Behring in 2003. Octapharma acquired the plasma products business of the Swedish-based manufacturer Biovitrum in 2002. In late 2002 Baxter acquired the alpha-1 antitrypsin product Aralast™, 42 plasma collection centres and a testing laboratory from Alpha Therapeutic Corporation (Mitsubishi Pharma), and in 2003 Grifols purchased Alpha's Los Angeles fractionation plant and the company's operations in key Asian markets. Bayer sold its plasma products division to a consortium of investors in 2005 and the business is now known as Talecris Biotherapeutics. The American Red Cross (ARC) left the plasma products market in 2005.

Baxter subsequently closed 26 of its own plasma collection centres and 38 collection centres acquired from Mitsubishi Pharma, as well as a 600 000 litre-capacity fractionation plant at Rochester, Michigan. The rationalisation involved an initial loss of 2500 positions worldwide.<sup>5</sup>

CSL's economies included the closure of 35 collection centres in the United States, a reduction in plasma collections by 1 million litres, and a reduction in plant throughput by 1.1 million litres. ZLB Behring (now known as CSL Behring) closed its Vienna plant and moved production to Marburg in Germany.

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2 See 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.

3 See J. Curling & C. Bryant, 'The Plasma Fractionation Industry: New Opportunities to Move Forward?', *BioProcess International*, vol. 3, no. 3, March 2005, p. 20.

4 See Aethena Global, *The Four Stages of Recovery: Shock – Consolidation – Aftershock – Growth*, The Ground Rounds: Insights and Intelligence for Healthcare, Healthios, Northbrook, Ill., [2005], p. 2, <<http://www.healthios.com/institute/Grand%20Rounds%20Plasma%20Therapeutics.pdf>>.

5 Baxter staff retrenchments increased to 4000, or 8% of the company's global workforce, in 2004.

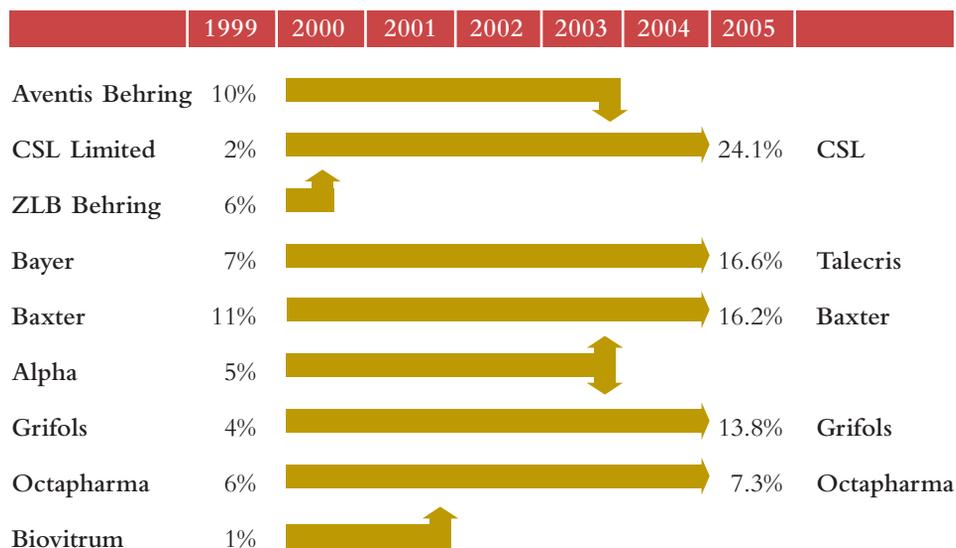
**Table 3.2** Key transactions in the plasma therapeutics industry, 1997–2005

Date	Enterprise	Venture
Jan 1997	Baxter	Purchases Immuno International AG
Jan 1999	Octapharma	Purchases Aventis Behring plant at Lingolsheim, France
Jan 2000	Baxter	US\$150 million upgrade to its plasma facilities at Glendale and Vienna
Jul 2000	CSL Limited	Purchases assets of ZLB, to form ZLB Bioplasma AG
Feb 2001	Baxter	Purchases Sera-Tec Biologicals
Jul 2001	ZLB Bioplasma	Purchases 47 plasma collection centres and laboratory facilities operated by Nabi in the United States
Mar 2002	Grifols	Purchases SeraCare's 45 plasmapheresis centres
Jul 2002	Octapharma	Purchases Biovitrum's plasma products business (Sweden)
Dec 2002	Baxter	Purchases Aralast™ and 42 plasma collection centres from Alpha Therapeutic Corporation (Mitsubishi Pharma)
Jan 2003	Octapharma	Purchases Probifasa SA (Mexico)
Mar 2003	Baxter	Acquires European distribution rights for WinRho™ (Cangene)
Jul 2003	Grifols	Purchases Alpha Therapeutic Corporation plant, Los Angeles, and Japanese trading entities
Dec 2003	CSL Limited	Purchases Aventis Behring's plasma products business
Jan 2004	Cangene	Announces expansion of fractionation facility
Aug 2004	Sanquin	Enters into manufacturing agreement with Finnish Red Cross with respect to plasma collected in Finland
Mar 2005	Baxter	Enters into new long-term supply agreement with American Red Cross and terminates manufacturing agreement
Mar 2005	Baxter	Acquires US distribution rights for WinRho (Cangene)
Apr 2005	Talecris	Forms as a result of acquisition of Bayer plasma products business
May 2005	CSL/ZLB Behring	Manufacturing agreement with ARC expires
Nov 2005	Octapharma	Enters into management contract to operate plasma fractionation plant owned by NSTOB, the blood transfusion service founded by the German Red Cross

Source: Derived from information in: Aethena Global, *The Four Stages of Recovery: Shock – Consolidation – Aftershock – Growth*, The Ground Rounds: Insights and Intelligence for Healthcare, Healthios, Northbrook, Ill., [2005], p. 5, <<http://www.healthios.com/institute/Grand%20Rounds%20Plasma%20Therapeutics.pdf>>.

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**Fig. 3.1** Plasma fractionators: mergers and acquisitions, 1999–2005. The percentages represent share of global fractionation capacity.



Source: Adapted from Baxter, with Marketing Research Bureau 2005 data incorporated.

News reports of plans by Grifols and Talecris to list on the share market appeared in early 2006.<sup>6</sup> Negotiations for the merging of the production activities of Sanquin and Biotest, a small German commercial fractionator, were announced in May 2006.<sup>7</sup>

The most significant expansion activities within the plasma fractionation industry for the period 1997–2005 are identified in table 3.2; outcomes in terms of increased share of global fractionation capacity are detailed in figure 3.1.

The announcement by Sanquin and Biotest that opportunities for cooperation are being explored is a demonstration that the boundaries between the not-for-profit and commercial sectors are becoming increasingly blurred. Some not-for-profit organisations have the capacity to sell surplus products to support financial viability. Others look to securing toll fractionation agreements as a means of increasing capacity utilisation and contributing to fixed operating costs.

### Key fractionators

CSL Bioplasma represents a unique case, in that its domestic operations in Australia retain historical elements in terms of market focus and product range. The CSL Bioplasma plant at Broadmeadows, Victoria, was originally designed to provide an ongoing domestic fractionation capacity for the benefit of Australia. The intention was to operate a state-of-the-art facility, capable of meeting all of Australia's growing requirements for fractionated products, using domestic plasma. Initially conceived as a

<sup>6</sup> See 'New Blood on CSL's Block', *Australian Financial Review*, 10 April 2006, p. 18.

<sup>7</sup> See Biotest, *AD-Hoc-Announcement §15 WpHG: Biotest and Sanquin Plan a Strategic Alliance in Plasma Products*, media release, 3 May 2006, Biotest, Frankfurt, <[http://www.biotest.de/ww/en/pub/folder\\_ag/news/03\\_05\\_2006\\_biotest\\_and\\_sanquin.htm](http://www.biotest.de/ww/en/pub/folder_ag/news/03_05_2006_biotest_and_sanquin.htm)>.

not-for-profit undertaking, the Broadmeadows plant now forms part of a major international fractionation business – but fulfils a role that has fundamentally not changed. The plant is still dedicated to meeting the needs of the Australian community as a first priority, although it now also provides toll fractionation services for smaller neighbouring regional markets. This role contrasts with that of CSL Behring, which operates as a large multinational player and depends on the supply of plasma obtained from paid donors in the United States and from paid and unpaid donors in Europe.

Baxter is a large and well-respected, multi-divisional, multinational corporation engaged in the manufacture of products for supply to the global health care market. Baxter has a global presence and approximately 47 000 employees, and the company's products are used in over 100 countries.

Talecris Biotherapeutics is a new company, formed in 2005 as a result of the acquisition of Bayer HealthCare Biological Products Division's US plasma operations, based in North Carolina, and the Precision Pharma Services fractionation plant, located on Long Island, New York. The corporate vision of Talecris is to be recognised as a global leader in the development and delivery of premium protein therapies. In 2005 Talecris had the second-largest fractionation capacity in the world.

Grifols is a privately owned plasma fractionation company headquartered in Barcelona, Spain. With a production capacity of 3.4 million litres annually, Grifols is one of the five largest global fractionators. The company maintains fractionation plants in Spain and in the United States.

Octapharma is a privately owned company headquartered in Switzerland and is one of the largest privately owned plasma product suppliers in the world. Since its founding in 1983, Octapharma has become one of the key players in the global plasma products market. With sales offices and representation in over 70 countries, Octapharma competes successfully against much larger, publicly listed corporates and has a stated objective to be the fifth-largest fractionator globally.

## Operational factors

### Plasma collection

There are two distinctly different avenues for the procurement of starting plasma: one based on the collection of voluntary, non-remunerated donations of whole blood and plasma, and the other based largely on the collection of plasma by apheresis, from paid donors. The fractionation firms with large-scale manufacturing operations in the United States and Europe acquire the bulk of their starting plasma requirements from paid donors. The obtaining of starting plasma is estimated to represent 40% of total plasma fractionation costs.<sup>8</sup> Collection costs include payments and other forms of reimbursement to donors, the cost of equipment and consumables, plus staffing and operating costs at collection centres. The open market price for starting plasma varies substantially (US\$80–\$135 per litre), depending on where plasma is collected and the method of collection used.<sup>9</sup>

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<sup>8</sup> See National Blood Authority, *NBA Supply Arrangements for Blood Products and Services*, National Blood Authority, Canberra, 2006, <<http://www.nba.gov.au/CONTRACTS/supplier.htm>>; and Curling & Bryant, p. 19.

<sup>9</sup> See National Blood Authority, *NBA Supply Arrangements for Blood Products and Services*, <<http://www.nba.gov.au/CONTRACTS/supplier.htm>>.

### Upkeep of fractionation plants

The difficulties and high capital cost associated with constructing and licensing a greenfield fractionation plant discourage this means of building capacity. Instead, fractionators undertake continual investment to improve and upgrade existing plants, in order to increase capacity, to improve the safety, quality and yield of products and to meet regulatory requirements. Companies do not enjoy the luxury of manufacturing from fully depreciated plants, as reinvestment is a constant process in the industry.

### Range of products manufactured

Although fractionators seek to maximise product range as well as yield, no manufacturer presently produces the complete range of available plasma derived products.<sup>10</sup> Production of hyperimmune immunoglobulins is particularly specialised. CSL Bioplasma currently produces and supplies all of Australia's requirements for hyperimmunes, using a small dedicated Cohn plant at the Broadmeadows facility. No other single manufacturer produces all of the hyperimmune products required for the Australian market. Hyperimmune manufacturing is low-volume, high-value and of limited commercial interest to most fractionators. Hence smaller, more specialised organisations, such as Cangene, Nabi and not-for-profit fractionators, tend to produce these products.

## Comparison of plasma therapeutics sector and pharmaceuticals industry

Compared with the costs associated with pharmaceutical production, the fixed cost structures encountered by plasma fractionators are of a high order. Relatively high costs are imposed on fractionators by the need to comply with increasingly rigorous regulatory requirements. These involve ever more complex manufacturing processes, which, in turn, require continuing and additional regulatory oversight.

Cost pressures have created an incentive for fractionators to make full use of their available starting plasma by deriving from it the maximum number of saleable products. Fractionators usually manufacture IVIg, albumin and Factor VIII, plus a number of other plasma derived products, the aim being to spread the fixed cost burden across a broad product range. A manufacturer will face difficulties if, because its product range is narrow, it cannot maximise return from each litre of plasma, through the realisation of competitive in-market prices. Furthermore, fractionators have an interest in achieving maximum throughput in plants in order to optimise efficiency and to generate an acceptable return on capital expenditure. Manufacturers may resort to marginal pricing for toll fractionation assignments so as to soak up any under-utilised plant capacity.

In addition to the high fixed cost structures affecting fractionators, there are other significant differences in cost structure between the plasma therapeutics sector and the pharmaceutical industry:

- 40–45% of the total cost of producing plasma therapeutics is accounted for by the cost of raw materials, whereas raw materials make up only 10% of the total cost of producing pharmaceuticals. The costs of plasma collection and testing are reflected in the open market prices for plasma, which, as noted earlier, vary between US\$80 and US\$135 per litre.

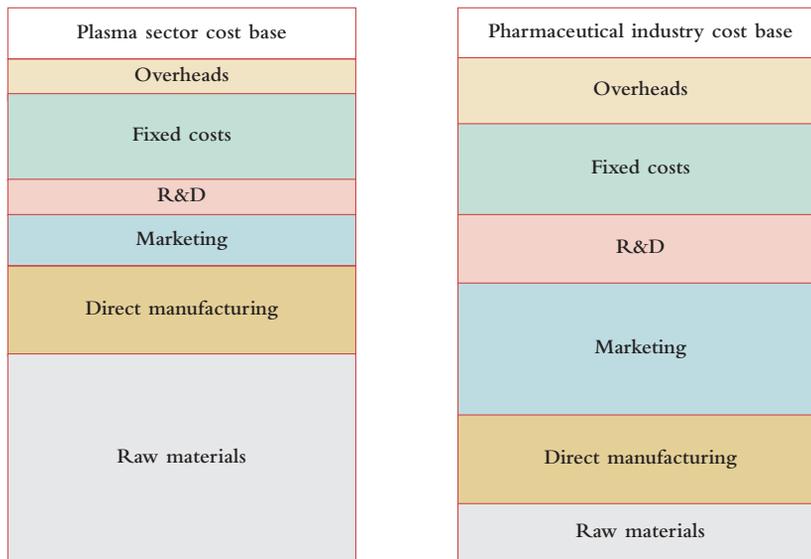
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<sup>10</sup> See National Blood Authority, *Supply of Defined Blood Products: Future Arrangements – A Discussion Paper, 2005*, p. 7; also available online at <[http://www.haemophilia.org.au//sb/modules/news/attachments/18/DISCUSSION %20PAPER%20-%20SUPPLY%20OF%20DEFINED%20BLOOD%20PRODUCTS%20-%2018%20July%202005.pdf](http://www.haemophilia.org.au//sb/modules/news/attachments/18/DISCUSSION%20PAPER%20-%20SUPPLY%20OF%20DEFINED%20BLOOD%20PRODUCTS%20-%2018%20July%202005.pdf)>.

- Production lead times are longer for plasma products, the manufacturing process is generally more complex, and there is more intense regulatory surveillance.
- Patient populations for plasma derived products are small but the average cost of treatment may be substantial in dollar terms.

Figure 3.2, based on a Plasma Protein Therapeutics Association presentation at the International Plasma Protein Congress held in Prague in March 2006, contrasts the cost structures of the pharmaceutical industry and the plasma fractionation sector.

**Fig. 3.2** Cost comparison for plasma sector and pharmaceutical industry



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

## Plasma fractionation today

A broad distinction can be made between fractionation plants that serve large, global markets, and plants that serve the needs of national markets. The former generally focus on throughput volume and specialise in a relatively small number of products. The latter generally focus on an expanded product range so as to meet the majority of the needs of a single domestic or regional market.

Among the larger fractionators that operate several facilities, there is a trend towards plant specialisation, as distinct from the production of a comprehensive range of plasma derivatives at all plants. Plant specialisation means that individual plants are dedicated to the manufacture of one particular product or group of products. Economies of scale can be realised by specialising in this way, despite additional logistical costs. Baxter and CSL Behring are examples of global fractionators that transport fractionation intermediaries (components of plasma separated during the manufacturing process) between plants that specialise in the manufacture of one product or group of related products.

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By contrast, some global fractionators maintain a network of smaller-capacity plants and manufacture a full suite of products at each of them. The rationale for this arrangement is to ensure continuity of supply of all products, even if one plant must cease production for any reason. This model is employed by Octapharma, governing production at its three European plants. The company's view is that this paradigm provides a greater level of flexibility than the specialised plant model, and permits an ongoing process of developing efficiency gains through an internal competitive environment.

CSL Bioplasma also operates according to a stand-alone model, whereby the one plant manufactures a complete product range and undertakes all stages of production, from primary extraction right through to the finished product. CSL describes this model as 'tailored self-sufficiency'.<sup>11</sup> In the case of interruption to supply, CSL Bioplasma would rely on its sister organisation, CSL Behring, to fill any gaps in supply.

### Manufacturing models for plasma fractionation

Trends with respect to manufacturing models within the global plasma products market are very much driven by country-specific objectives. Increasingly Europe is opening up to greater movement of starting plasma and finished plasma products across national borders, although nation-specific regulations remain in place. Due to factors such as increasing harmonisation of regulation, advances in logistics and communications, and economic pressures, some smaller countries have moved from a national fractionation model to toll fractionation. The list of countries relying on toll fractionation includes Belgium, Canada, Denmark, Finland, Hong Kong, Malaysia, New Zealand, Norway, Poland and Singapore. Brazil is an example of a large developing country that has attempted to build a domestic fractionation capacity in recent years but has failed, due to technical difficulties encountered. Brazil now relies on offshore toll fractionation, while seeking to reorganise for future domestic production.

As standards of medical diagnosis and care continue to rise, many developing countries are experiencing increased demand for plasma derived products and for recombinants. The high costs involved in securing these products, however, mean that there cannot be unlimited access to them. Economic capacity thus influences the procurement as well as the extent of clinical usage of plasma products, resulting in sub-optimal treatment for many patients in developing nations.<sup>12</sup>

In order to meet different countries' requirements for plasma derived products, the industry has become organised along lines that reflect marketplace needs. Countries with developed economies are the big consumers of plasma products, and this factor has encouraged the emergence of large-scale fractionation capacity in the United States and Europe. Developing economies and markets draw their product requirements either from the larger-scale fractionators or from small-scale domestic fractionators.

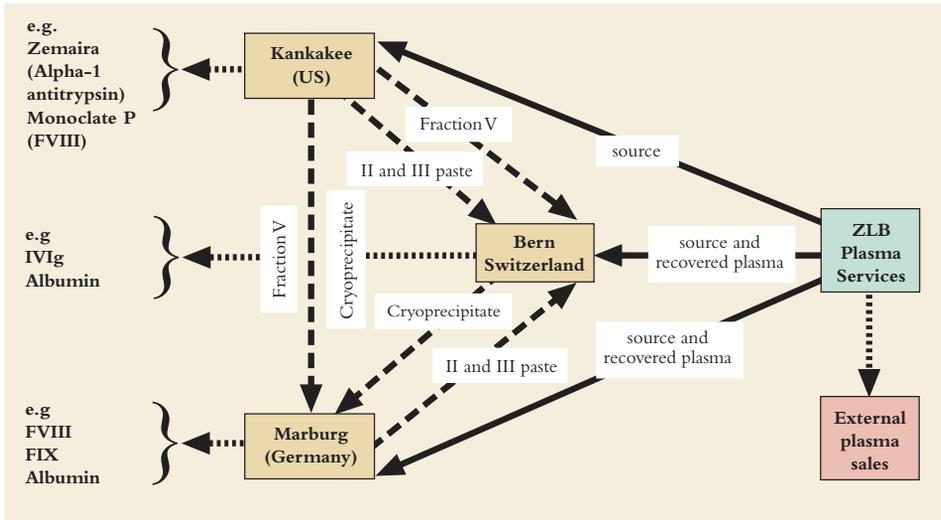
Large-scale, multiple-site fractionators fall into one of two categories, according to the manufacturing model preferred. The 'centres of excellence' model, as illustrated in figure 3.3, is employed in various forms by CSL Behring and by Baxter.

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<sup>11</sup> CSL Limited, submission to Plasma Fractionation Review, 2006, p. 20.

<sup>12</sup> See A. Farrugia, 'Safety and Supply of Haemophilia Products: Worldwide Perspectives', *Haemophilia*, vol. 10, no. 4, July 2004, pp. 327–33.

**Fig. 3.3** Centres of excellence model



Source: CSL Limited, presentation to Plasma Fractionation Review Committee, July 2006.

The diagram describes the flow of plasma raw material and intermediaries between plants that specialise in the production of particular products (e.g. immunoglobulins, clotting factors or specialty products). Plasma that has been collected by a collection service is delivered, either as source plasma or as both source and recovered plasma, to multiple plants for primary extraction. Each plant then retains the intermediaries relevant to its specialisation and passes the remaining intermediaries on to other plants, as appropriate to their individual specialisations, for final processing to finished product stage.

According to CSL Limited, the 'centres of excellence' in its network undertake the following R & D activities:

- Marburg: 'development of coagulation therapies, along with critical care and speciality products'
- Bern: 'immunoglobulins, production methods and safety standards'
- Melbourne: 'development of state-of-the-art purification technologies for plasma products'
- Kankakee: 'continuous improvement of our Alpha-1-Proteinase Inhibitor (Alpha-1-PI) product'.<sup>13</sup>

A multi-centre model would not be readily adaptable to Australia's relatively small fractionation needs and it is for this reason that CSL Bioplasma sits outside the 'centres of excellence' paradigm.

Another model is represented by Sanquin (Netherlands), Laboratoire Français du Fractionnement et des Biotechnologies (LFB) (France), and Bio Products

<sup>13</sup> CSL, *Research & Development*, CSL, Melbourne, 2006, <[http://www.csl.com.au/R\\_+\\_D.asp](http://www.csl.com.au/R_+_D.asp)>.

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Laboratory (BPL) (United Kingdom). These not-for-profit fractionators are primarily structured to supply domestic markets. Sanquin is a benevolent foundation that is mandated by the Netherlands Government to provide all blood services for the Netherlands community. LFB and BPL are predominantly state-owned bodies, operating under the auspices of the ministries of health in France and the United Kingdom respectively.

In countries where there is an open market for finished plasma products, the not-for-profit sector is finding it increasingly difficult to compete with the larger commercial-scale operations. The result has been a blurring of the boundaries between commercial fractionation and not-for-profit fractionation, with not-for-profit fractionators increasingly being driven into commercial activities, including toll fractionation and exporting, in order to survive financially.

Sanquin is undertaking toll fractionation for Belgium and Finland and is looking to form a joint venture with the small German commercial fractionator Biotest, in order to upscale fractionation capacity. The operations of BPL are under review by the British Government, but in any case BPL is looking to export markets in developing countries to provide half of its revenue stream. LFB is already engaged in toll fractionation for four other countries, and is seeking to add to its portfolio of toll fractionation clients so as to increase the organisation's international franchise and absorb its under-utilised capacity.

It is important to note that throughout Europe the market for plasma derived products is open. This means that hospitals or their proxies are free to purchase any brand of product that is registered for marketing. In Australia, by contrast, domestically manufactured products must be used as a first priority, and imported product is supplied only as a contingency in the event of shortages.

Three large companies dominate the US market: CSL Behring, Baxter Biosciences and Talecris. CSL Behring and Baxter Biosciences operate under the 'centres of excellence' model and provide products to the US market that are either manufactured domestically or imported from Europe. Talecris, which operates under the stand-alone model, only markets products that are manufactured domestically. Talecris also toll fractionates for Canada.

Countries outside the United States and Europe acquire plasma products by various means. China and Japan have domestic fractionation capacity but are finding it necessary to import some products. Russia is currently constructing a domestic fractionation facility. Brazil, as noted previously, has attempted to operate a domestic facility but more recently has been dependent on toll fractionation and imported products. Most other countries rely on products marketed by the large- to medium-sized global manufacturers, which include Grifols (Spain and the United States) and Kedrion (Italy).

The World Health Organization has estimated that 15% of the world's population consume 91% of the world's output of pharmaceuticals (by value),<sup>14</sup> and plasma products are no exception to this pattern: usage levels in any given country broadly correspond to that country's standard of living. It will be of interest to see if rapidly growing economies such as China and India, as part of a greater investment in their health systems, choose to concentrate on domestic collection and fractionation of

plasma, or instead purchase growing quantities of plasma derived products on the open global market. Rapid increases in demand could well bring about pronounced shortages and price increases (particularly with respect to IVIg, the demand for which is continuing to grow strongly).

Differences from country to country in terms of patterns of clinical care, health care financing by government, and industrial infrastructure, have led to the development of differing national models for the supply of plasma derived products. These models may be summarised as follows.

### **Self-sufficiency models**

For some time there has been a widespread view that governments have a responsibility to their own citizens, and to citizens of other countries, to use domestically sourced blood and blood products as much as possible. This viewpoint was articulated in a 1975 World Health Assembly (WHA) resolution, WHA28.72, to which Australia is a signatory. The resolution, driven by concerns regarding the exploitation of developing countries by commercial interests, and the consequent potential for trade in infected blood products, exhorts member states of the WHA:

- (1) to promote the development of national blood services based on voluntary nonremunerated donation of blood;
- (2) to enact effective legislation governing the operation of blood services and to take other actions necessary to protect and promote the health of blood donors and of recipients of blood and blood products.<sup>15</sup>

Policies such as these have been widely regarded as promoting public confidence in the blood systems of countries that adopt them. This confidence is critical to ensuring the sustainability of national blood systems, which rely on community goodwill and on the motivation of individuals to donate. Perceptions about safety and security of supply, together with concerns that voluntarily donated blood should not be used for commercial gain, have perpetuated the tenets of the WHA resolution.

Since the resolution was adopted, the plasma products industry has become increasingly globalised and subject to increasingly stringent regulatory regimes. These have been implemented with respect to donor eligibility as well as testing and viral inactivation, permitting international movement of products that are safe and efficacious. However, for reasons relating to security of supply, together with ethical and humanitarian considerations, there is a prevailing view that countries should avoid making disproportionate demands on the blood systems of other countries.

National health systems strive to attain degrees of self-sufficiency that suit their particular economic and policy objectives. Governments in several European countries and elsewhere, including Japan and Australia, have established, or have supported the building of, domestic fractionation infrastructure. The resulting national fractionation plants are comparatively small and do not offer the same economies of scale as the large commercial plants, which are located primarily in the United States and throughout Europe. As noted

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<sup>15</sup> World Health Organization, *Twenty-Eighth World Health Assembly, Geneva, 13–30 May 1975: WHA28.72 Utilization and Supply of Human Blood and Blood Products*, World Health Organization, Geneva, 1975, <<http://www.who.int/bloodsafety/en/WHA28.72.pdf>>.

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earlier, some national fractionators, among them CSL Bioplasma, Sanquin and LFB, accommodate toll fractionation customers so as to better utilise capacity and to alleviate high fixed cost burdens.

### Toll fractionation models

Due to the substantial financial resources and technical expertise required for the establishment and maintenance of a domestic fractionation industry, a number of smaller developed nations have elected to rely on toll fractionation arrangements, sometimes referred to as contract fractionation. Under these schemes, an entity (typically a government agency or a blood collection organisation) enters into a contract with an external fractionator, for the fractionation of plasma collected in the originating country. Products manufactured from this plasma are then returned to the originating country (some toll fractionation contracts may specify that the fractionator is free to sell any excess products not required by the country from whose plasma they have been manufactured).

Toll fractionation arrangements operating today include those for:

- Belgium (Sanquin)
- Canada (Talecris)
- Denmark (CSL Behring)
- Finland (Sanquin)
- Malaysia, Singapore and Hong Kong (CSL Bioplasma)
- New Zealand (CSL Bioplasma)
- Norway (Octapharma)
- Poland (Baxter).

For many years the American Red Cross had a toll fractionation arrangement with Baxter, whereby plasma collected by the ARC was processed by Baxter and returned as finished product, but this arrangement was discontinued in 2005 when the ARC exited the plasma products market in the United States. (Today Baxter purchases starting plasma from the ARC for fractionation.)

The advantages of toll fractionation for a country entering into such an arrangement include the assurance of an adequate supply, at constant prices, of products that would otherwise need to be purchased on the open global market. There are, however, dimensions to a toll fractionation arrangement that do not apply to domestic fractionation. These include regulatory oversight requirements specific to contract fractionation, longer lines of supply, and the need for additional steps to ensure continuity of supply from an external fractionator.<sup>16</sup> Toll fractionation agreements typically specify minimum standards of performance, including yield.

### Commercial models

In the United States, a system whereby voluntary, non-remunerated donors donate whole blood for the not-for-profit provision of fresh blood products coexists with a system whereby remunerated donors provide apheresis plasma (source plasma) for fractionation. In the commercial plasma supply sector, which relies heavily on the

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collection of source plasma from remunerated donors, there are three main groups involved: collection agencies, brokers, and fractionators (some of which operate their own collection centres). The collection agencies and brokers sell plasma obtained via apheresis to fractionators in the United States and overseas. Brokers also purchase and market recovered plasma, collected from voluntary donors attending whole-blood collection centres. Fractionators market finished plasma products either directly to user institutions or through collective purchasing agencies. There are supply-driven variations in the prices of products, but buyers have a wider choice of brands than in other national markets, where choice of brand may be limited by availability, which can in turn be determined by supply policy.

The US commercial plasma products market is thus characterised by multiple suppliers and numerous purchasing agencies, in an environment in which public sector agencies do not play a dominant role with respect to the procurement of plasma fractionation services. Vertical integration is also a feature of the US industry, with some fractionators maintaining substantial plasma collection networks.

In other countries (such as Australia), finished plasma products may be sourced on the open global market, but only when they are needed to supplement domestically sourced product supply. Nations with neither a domestic fractionation capacity, nor a toll fractionation arrangement in place, obtain all of their plasma products on the open global market.

With an output that exceeds domestic requirements, the United States is the leading exporter of plasma derived products. Reliance on products purchased on the open market, however, can expose purchasers to the risks of scarcity of supply and price fluctuations (for instance when demand outstrips supply or when there are disruptions in supply as a result of regulatory sanctions). The product recalls and plant closures that affected US production during the late 1990s caused serious price increases and product shortages – particularly in respect of IVIg – both domestically and in export markets that depended on US supply.

While many countries are self-sufficient in fresh blood products, only the United States is self-sufficient in plasma for fractionation. The US system of remunerated plasma collections delivers more starting plasma than is required to meet the domestic need for finished products: just over one third of the plasma collected is used domestically, and the remainder is available for export as starting plasma, plasma intermediaries, and finished product.

With the United States accounting for approximately 70% of the plasma collected globally, a significant number of countries draw in part on US-sourced plasma or finished plasma products.

The United States exports significant quantities of plasma to Europe, where total collections are insufficient to meet both domestic demand and external demand for finished products.

Canada is an example of a country that draws substantially on US plasma products, while at the same time using finished products manufactured from plasma collected within its own borders and fractionated under the terms of a toll fractionation arrangement.

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A further model is represented by the fractionation arrangements of the Irish Republic: the Swiss-based company Octapharma, acting on behalf of Ireland, purchases plasma on the US and German open markets and then fractionates it into products for consumption in the Republic.

The British Government maintains a network of plasma collection sites in the United States so as to be able to meet UK domestic requirements (all domestic plasma in the United Kingdom is currently discarded, due to risks associated with variant Creutzfeldt-Jakob disease (vCJD)).

The risks of blood-borne transmission of infectious agents were not fully comprehended until the emergence of HIV/AIDS and hepatitis C in the early 1980s. Attention was then focused on the safety, quality and efficacy of blood and blood products, triggering changes in donor selection processes, in testing regimens, and in fractionation procedures (which now include multiple viral-elimination steps). The potential risk of transmission of vCJD through plasma products is a more recent concern.

At the same time, developments in production technologies, communications and transportation have led to increased globalisation of the fractionation industry. The use of electronic monitoring devices and bar coding systems, and improved logistics, mean that it has become feasible for starting material, finished products and even plasma intermediaries to be transported over long distances without significant risk to product integrity. There has also been an increased harmonisation of regulatory standards from country to country, and greater levels of liaison among industry participants, to ensure that the international movement of plasma products takes place safely and securely.