

The Plasma Fractionation Industry

New Opportunities To Move Forward?

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Shortly after the turn of the millennium, Australian fractionator CSL Ltd. acquired the Swiss plasma plant at ZLB, Bern (Central Laboratory of the Swiss Red Cross Blood Transfusion Service). Two years later, the US plasma fractionation industry entered the year 2003 with an announcement that the proposed merger between Aventis Behring and Bayer's plasma operations would not happen. In August 2004, soon after CSL completed its acquisition of Aventis Behring, the newswires buzzed with speculation over Bayer's long-awaited divestment of its plasma business in Clayton, NC. On 14 December 2004, Cerberus and Ampersand agreed to acquire that Bayer unit.

Such movements seem commonplace in an industry sector that has endured consent-decrees, battled with product shortages of both plasma-derived and recombinant products, faced dramatic drops in product pricing, and all but lost a market for albumin. Raw material (plasma) costs have risen significantly, and processing costs rise with each incremental addition of safety measures such as inventory hold and plasma pool testing.

However, CSL Ltd (www.csl.com), now the holding company for ZLB Behring and the world's largest fractionator with a 25% market share

COHN FRACTIONATION

The development of methods for plasma protein fractionation was driven by a need for human albumin in World War II and the requirement to isolate diphtheria and tetanus antibodies from horse serum.

E. J. Cohn and his many coworkers published their landmark paper describing ethanol fractionation in 1946 (1). Their paper was 43rd in a series entitled *Studies on Plasma Proteins* from Harvard Medical School. The first use of ethanol fractionated albumin was to treat casualties at Pearl Harbor in 1941.

The fractionation industry is now driven by the demand for IgG to treat immune deficiencies and recombinant as well as plasma-derived Factor VIII for hemophiliacs. Nonetheless, the industry standard backbone is still "Cohn fractionation" with chromatography and membrane technologies, integrated with viral inactivation, dominating side-stream fractionation.

REFERENCE

1 Cohn EJ, et al. Preparation and Properties of Serum and Plasma Proteins, IV: A System for the Separation into Fractions of the Protein and Lipoprotein Components of Biological Tissues and Fluids. *J. Am. Chem. Soc.* 62, 1946: 459-475.

(with operations in Switzerland, Germany, and the United States), reported net profit after tax of 13% on revenues of US\$1.65 billion for the past financial year, ending 30 June 2004. Importantly, CSL's cash flow increased significantly, and R&D expenditure was up 11% to over US\$100 million. As another important industry indicator, approval of new plasma products indicates no lack of innovation. New, higher yielding side-stream processes also indicate innovation within limits, intended or not, frequently set by regulatory authorities.

INDUSTRY CONSOLIDATION

Major structural changes of the North American–European plasma fractionation axis are shown in the “Plasma Industry Changes 2003 and 2004” box. Clearly, major chemical-pharmaceutical companies are seeking to exit the business, whereas dedicated plasma companies such as CSL Ltd., which continues to divest non-core business, and Probitas Pharma (Grifols) are eager to consolidate and strengthen their positions. Increasingly, raw material (plasma) follows the laws of commodity markets as we witness the acquisitions and divestments of collection centers across the United States.

Past and current chairs of the Plasma Protein Therapeutics Association (PPTA, www.plasmatherapeutics.org) have successfully differentiated the plasma industry from the pharmaceutical industry. For example, raw material costs account for around 45% of the units on an income statement in the plasma industry compared with 5% in the pharmaceutical industry (1). Quality plasma costs have risen 40% over the past seven years, and nucleic-acid testing alone adds US\$5–15 per liter of plasma (2). Although recalls and withdrawals have declined dramatically, inventory hold costs the industry another US\$33 million per year (2).

In his 2004 analysis of the industry, the PPTA Chair Peter Turner notes that “US and European demand for IVIG

PLASMA INDUSTRY CHANGES 2003 AND 2004

2003

Bayer and Aventis halt plans for a merger of their plasma products businesses.

CSL announces preliminary negotiations with Aventis concerning the acquisition of Aventis Behring.

Baxter announces plans to close 26 of its 120 plasma collection centers in the United States as well a 700,000-L plant in Michigan. Plasma collected and fractionated will drop from 4.6 million liters to 4 million liters, and 800 jobs will be eliminated.

Probitas Pharma completes acquisition of assets of Alpha Therapeutic from Mitsubishi Pharma.

Octapharma completes acquisition of Mexican fractionator Probitas SA de CV.

Aventis Bio-Services sells 21 of its 80 plasma collection centers to International Bioresources.

Bayer initiates divestment of the plasma operations of its Biological Products Division. Plasma product sales were €679 million in 2002. Bayer employs 1350 people at its Clayton, NC, facility.

CSL and Aventis sign a definitive agreement, creating a new entity, ZLB Behring, for US\$925 million. Aventis Behring generated €1.068 billion in sales in 2002 and employs 5800 people worldwide.

2004

Baxter further reduces fractionation capacity by around 13% (400,000 L annually and closure of further collection centers).

ZLB Behring, formerly Aventis Behring, closes 35 collection centers, reducing collection volume by one million liters and leaving 65 centers in operation. Plasma throughput at the Kankakee, MI, facility will be reduced, the Vienna plant closed, and production transferred to Marburg, Germany. ZLB Bioplasma's facility will implement improved use, and the combined capacity of CSL's facilities will be reduced from 4.2 million to 3.1 million liters. CSL expects to save US\$100 million in operating costs.

Probitas Pharma is forced to suspend its IPO because of weak investor demand. The company expects to double its sales from US\$1.26 billion in 2003 over five years, achieving a 10% global market share.

Bayer's short list of bidders for its plasma fractionation business includes investment firms Bain Capital and Carlyle Group. Cerberus is also bidding, and the American Red Cross is reported to have an interest. On 14 December, Cerberus Capital and Ampersand Ventures agreed to buy the business for over US\$590 million. The new company thus created, NPS Biotherapeutics, Inc., will also incorporate Precision Pharma. Bayer's plasma products generated sales of US\$739 million with a pretax loss of US\$426 million in 2003. Sales in FY2004 were €481 million.

The Finnish Red Cross, which decided to discontinue fractionation in 2003, enters an agreement with Sanquin for the manufacture and supply of plasma products for Finland's market. Intermediates will be produced in the Belgian Red Cross fractionation facility and finished products processed in Amsterdam.

[intravenous immunoglobulin] has been met, and prices have fallen 20–25% in two years, the price of albumin has halved in three years, substitution of recombinant Factor VIII for plasma-derived product continues, and there is greater access to alpha₁-protease inhibitor” (3).

In this climate, industry consolidation and realignment are understandable, but widely disparate access to plasma protein therapies remains unaddressed across the globe. Among the PPTA models for the future (3) are a

- Broad portfolio of high yielding products
- Global plasma reach selling three–four products/liter of plasma
- Efficient scale and competitive cost structure.

MORE PRODUCTS PER LITER OF PLASMA

Blood plasma is the most complex human-derived proteome. It contains 55–60% albumin and offers an exceptional dynamic abundance range (10 orders of magnitude) — from picograms/mL of interleukins up to 35–50 g/L range for albumin. Despite the plethora of true plasma proteins (secreted from solid tissues and immunoglobulins), tissue-leakage products, and temporary plasma passengers, only 289 proteins have been documented; about 100 are used in diagnostic assays and fewer than 20 as plasma therapeutics, with three proteins accounting for 80% of the revenue (4). Assessing opportunities for the future, Over (5) found only five new products in clinical trials in 2002. However, 2003 was an exceptional year for new approvals by CBER (www.fda.gov/cber/products.htm), as shown in Table 1.

It is striking that all those products are new variants of established products and that they were launched in the US market as an attempt to expand market share, competing against existing products. Significantly, products new to the market are absent from the list of approvals — such as plasmin, fibronectin, and apolipoprotein A-1.

Table 1: New, US, normal plasma and equivalent recombinant product approvals (BLA) in 2002–2004

Product	Manufacturer Approval Date	Indication	Claimed Benefit/Improvement
Aralast Alpha-1 Proteinase Inhibitor (API)	Alpha Therapeutic (now Baxter) 23 December 2002	API deficiency and evidence of emphysema	First alternative to Prolastin; patient choice
Crosseal Fibrin Sealant	Omrix (Distr.: American Red Cross) 21 March 2003	Hemostasis in patients undergoing liver surgery	Ease of preparation and use
Zemaira Alpha-1-Proteinase Inhibitor (API)	Aventis Behring 8 July 2003	API deficiency and emphysema	Purity (≥90%), safety, efficacy, convenience; 15 min. infusion time (cf ≥30 mins for other products)
Advate rFactor VIII Plasma/Albumin Free Method	Baxter Healthcare 25 July 2003	Hemophilia A	Recombinant, no plasma products used in MAb production or as additives; no prion risk; tolerability, hemostatic efficacy; low inhibitor rate; easy to use
Gamunex IVIG, 10% by Chromatography Process	Bayer 27 August 2003	Primary immune deficiency and ITP	Unprecedented primary immune deficiency (PID) clinical results; anti-infective efficacy; new safety paradigm
Flebogamma IVIG	Instituto Grifols (Probitas Pharma) 15 December 2003	Primary immune deficiency	Liquid, ready-to-use
Octagam IVIG	Octapharma 21 May 2004	Primary immune deficiency	Only liquid and double virus inactivated IVIG that can be stored at room temperature (2–25 °C) up to 24 months; free from stabilizers

It also appears that the established industry is focused on highly competitive markets in which products are differentiated by manufacturers and distributors rather than by therapeutic effect. (That is changing, but on “benefit-to-patient” attributes such as ease of use, infusion time, shelf-life, and storage conditions.) The industry still tends to differentiate on safety, advocating added or improved viral clearance or prion safety as well as new manufacturing techniques.

A quick review of a plasma product distributor site — www.blooddiagnostics.com — illustrates the competitive nature of the market as well as the product offerings. Such an environment leads to price pressures and loss of revenue/liter of plasma as described by Rankin

(6). Despite lower pricing for IVIG, this product is likely to remain an industry driver, but added revenues from plasma-derived Factor VIII and alpha₁-protease inhibitor are mandatory for an industry that needs to invest in both plant and R&D. Net revenues (after the cost of plasma) from existing products per liter of plasma dropped from an all-time high of about US\$220 in 1999 to barely over US\$100 in 2003 (3). Among the various measures triggered by such a loss has to be the development of truly new products from plasma, not just incremental improvements to existing ones. This involves a paradigm shift and a new era of innovation that Christensen describes as a “disruptive technology” path (7).

HIGH-YIELDING PROCESSES

The Cohn backbone process was developed for albumin, so it is not surprising that this protein is obtained in high yield. Processes for other plasma proteins have been developed either by addition of (cryo-)precipitation or adsorptive technologies before using ethanol fractionation or by mainly chromatographic processing of fractions of the Cohn system, as in methods developed for alpha₁-antitrypsin. These processes are generally low yielding. Particularly, the low yield of IVIG caused (previously) major players Baxter and Bayer to implement significant improvement to purification from Fraction II + III. Considering the data in Table 2, there should be considerable room for improvement, but that would necessitate a radical change of processing technology, not generally attractive to an established industry bound by existing product licenses in the United States and around the world.

Table 2: Average process yields per liter of plasma from existing "Cohn" fractionation facilities.

Target Protein	Yield Cohn trunk (%)	Yield Cohn total (%)	Industry Average (1)	Industry Average (2)
Factor VIII by cryoprecipitation	40	18	140–270 IU	~200 IU
Factor IX	—	—	—	~350 IU
Immunoglobulin G	66	53	3–4 g	~3.5 g
Alpha1-protease inhibitor	23	15	—	~0.2 g
Albumin	95	86	22–28 g	~25 g

Yield figures in % are calculated from industry sources. The "Industry average (1)" figures are from "Contract Fractionation", World Federation of Haemophilia (reference 16). Industry average (2) estimates are from the PPTA (reference 17).

Affinity Chromatography: New technologies, which break the "S-curve" (7) development scheme, are unlikely to use differential solubility as the driver of separation. They are far more likely to use discerning technologies, commonplace in downstream bioprocesses, such as affinity

chromatography. This recently reviewed (8) technique is already used in many established process: in the purification of coagulation factors, for example, and in new processes such as that for plasmin. Such technologies allow for sequential adsorption, not precipitation, from the main

FDA GUIDANCE FOR INDUSTRY: SCREENING MATERIALS FOR HUMAN DONORS OF BLOOD AND BLOOD COMPONENTS

by James Reilly

In 2000, the American Association of Blood Banks (AABB) convened an Interorganizational Uniform Donor History Questionnaire Task Force at the request of the US Food and Drug Administration. The Task Force included a wide spectrum of constituents including blood center staff, survey design experts, an ethicist, and a statistician, as well as organizational members from AABB, America's Blood Centers, American Red Cross, Plasma Protein Therapeutics Association, US Department of Defense, and liaisons from the FDA, Centers for Disease Control and Prevention, and Canadian Blood Services. The goals of the task force were to

- Provide major improvement in blood donor screening
- Make the process more effective in capturing relevant blood-donor qualifying information
- Simplify the screening process
- Enhance recruitment and retention without sacrificing the safety of transfusion recipients.

In October 2000, the FDA and AABB cosponsored a workshop on "Streamlining the Blood Donor History

Questionnaire." The outcome of the task force and workshop proceedings was a series of donor-history questionnaire (DHQ) documents, which when implemented in their entirety effectively represent a comprehensive donor history screening system.

In April 2004 the FDA published a draft guidance titled *Acceptable Full-Length Donor History Questionnaire and Accompanying Materials for Use in Screening Human Donors of Blood and Blood Components*, which fully incorporated the DHQ documents including

- Blood Donor Educational Materials
- Full-Length Donor History Questionnaire
- Medication Deferral List
- Donor History Questionnaire
- User Brochure (including glossary, flow charts, and references).

AABB DHQ DOCUMENTS

Several important points need to be made regarding the DHQ documents and the FDA draft guidance.

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stream and the design of a backbone that targets the most needed plasma products.

GLOBAL ACCESS TO PLASMA PRODUCTS

With a supply crisis for IVIG an issue of the past, the overproduction of albumin, and the availability of new-generation Factor VIII presentations and alternative alpha₁-protease inhibitor (API) products, the majority of patients in North America, Europe, and other developed countries generally receive the products they need. Exceptions are that many hemophiliacs have yet to be on prophylactic treatment, and according to the Alpha-1 Foundation (www.alphaone.org), at least 90% of the 100,000 API-deficient patients in the United States remain undiagnosed and untreated — indicating a market opportunity if reimbursement policies would allow.

However, a very much larger and more global issue must be tackled. The World Health Organization (www.who.int) estimates that 15% of the world's population consumes

91% of the world's production of pharmaceuticals (9). Plasma product use is no exception to this. In 2000, the Americas and Europe consumed 83% of the plasma-derived Factor VIII and almost all the world's recombinant products (10). In the same report, Europe and North America accounted for about three quarters of the IVIG. For all products, the use of plasma derivatives in Africa is only about 1% of the total. With the current worldwide market for plasma-derived products stable at US\$5.8 billion, North America accounts for 37% and Europe for 30% (11). In contrast, North America accounts for 6.7% and Europe for 12% of the world population of just over six billion. Although the United States exports over 6.5 million liters of plasma (12), that is largely to facilities in Europe that either lack sufficient collection structures or are mandated not to use domestic sources because of possible vCJD risk (as in the United Kingdom).

The state of science and technology in developing countries

is a highly complex issue. The InterAcademy Council (IAC, www.interacademycouncil.net) notes that “the global reality is that many innovations fail to accrue to those who need them most.” Furthermore, “stronger science and technology capacity in the developing nations is not a luxury, but an absolute necessity if these nations are to participate as full partners in the world's fast-forming, knowledge-based society” (13).

The debate attempting to resolve issues related to plasma fractionation is not new with advocates of “self-sufficiency” (those who advocate local or national fractionation or contract fractionation at a distant-but-established fractionator). The December 1997 *Transfusion Today* contains six short articles on the subject (14), and the Gordian knot has not been untied over almost two decades. Central to the ability to produce safe and reliable plasma products is the existence of an adequate infrastructure for plasma collection, recently discussed by Farrugia (15). This is a necessity

FDA GUIDANCE FOR INDUSTRY (CONTINUED)

Blood Donor Educational Materials: This document provides a first layer of safety by familiarizing donors with the donation process and risks that result in deferral from donation. The document emphasizes the importance of accuracy and honesty in responses to screening questions.

Full-Length Donor History Questionnaire: The questionnaire is significantly different from previous questionnaires and is designed to be either donor self-administered or administered by direct oral screening, or computer-assisted screening. However, staff must be readily available to help donors in all cases. The DHQ uses “capture” questions that require additional action when a donor gives an unacceptable answer.

The questionnaire allows for addition of facility-specific questions to meet local regulatory requirements and questions that respond to temporary situations — such as those about severe acute respiratory syndrome (SARS). The DHQ documents incorporate screening questions based on cancer; organ, tissue, or bone marrow transplants; bone or skin grafts, and pregnancy (1). These go beyond the FDA requirements in 21 CFR Part 640.

Medication Deferral List: The most significant improvement to this component of the donor screening process was combining the various FDA-required permanent and temporary deferrals for medications. The document includes a rationale for the deferral, written in terms that donors can understand, and defines the period that a donor would be ineligible to donate. This approach allowed the replacement of multiple questions with a single question about medications in DHQ documents after review of the list. Facilities, at their option, can supplement the list with additional medications that have been identified as a result of local medical policies.

Donor History Questionnaire User Brochure: The brochure provides detailed instructions to facility screening personnel regarding how to administer the overall documents and system. The glossary, flow charts, and references provide follow-up questions to the “capture” questions and explain the process.

DHQ Document Evaluation and Review: The first donor-screening questionnaire was developed in 1953.

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independent of the volume of plasma made available for fractionation and independent of where fractionation is carried out. However, another side of the coin is that it must be possible within the healthcare system to diagnose, reach, and treat patients in need. Additionally, there needs to be political will and a regulatory environment to support provision of plasma products.

Import of finished products, although a possible short-term necessity, is neither a long-term, sustainable solution nor an economically satisfactory resolution for making plasma products available. The pros and cons of contract fractionation available in developing countries are well discussed in a World Federation of Haemophilia document (16). Neither solution encourages the development and establishment of biopharmaceutical processing at a local level.

Handed down from the UN Millennium Development Goals (www.un.org) and embedded in WHO thinking are ambitious targets for maternal and child health, infectious disease control, and access to essential medicines. Many mechanisms for achieving those goals depend on partnerships that serve to narrow the ever-widening gap between developing and developed nations. The IAC Report provides strong arguments and a framework for local development (13). In countries that benefit from the realization that supply of plasma products is a biopharmaceutical endeavor rather than an “altruistic” branch of blood transfusion, there is every reason to investigate establishing a national nongovernmental organization (NGO) or independent industrial venture. Creating world-class centers of excellence in biotechnology and bioprocessing can embrace establishing a plasma biotechnology

center responsible for the commercial production of plasma products.

If the gap between “have” and “have-not” nations is to be narrowed, the technology for such an industry needs to embrace current, best biopharmaceutical practice and embrace high yielding, competitive, and economically beneficial processes. In plasma product manufacturing, this is unlikely to be based on Cohn fractionation technology, but to rely on the standard unit operations of bioprocessing: chromatography and membrane separations together with the most recent and proven means of viral inactivation. R&D efforts will, therefore, probably be shared between the technology providers and the local, transfer recipients. When product development occurs at the local (national) level, patient needs can be targeted in the setting where the products are to be used.

FDA GUIDANCE FOR INDUSTRY (CONCLUDED)

Since that time, donor screening has become significantly more complex and time consuming. The DHQ documents represent a significant redesign and modified process. They were evaluated and modified as a result of testing that used a series of focus groups and one-on-one cognitive interviews (2).

REGULATORY REQUIREMENTS

The FDA draft guidance allows facilities to implement DHQ documents — if adopted in their entirety — with notice to the FDA only as a part of their annual report. There are two exceptions: Facilities choosing to modify the DHQ (except for deletion of certain questions not currently part of FDA requirements) must notify the FDA using the “Prior Approval Supplement” submission process; and those wishing to use the computer-assisted interactive interview procedure should consider this a “moderate change” and use the “Changes Being Effective in 30 Days (CBE30)” notice process. (Additional information on FDA reporting can be obtained at www.fda.gov/cbergdlns/donorhistques.pdf).

A SIGNIFICANT ADVANCEMENT

Donor screening is one of the pillars of transfusion medicine and related biological therapies safety. The FDA DHQ documents, when implemented in their entirety, represent a significant advance in donor screening systems.

Additional information and the DHQ documents can be found at www.aabb.org, click on “Pressroom, AABB Donor History Questionnaire.” The complete FDA Draft Guidance document can be found at www.fda.gov/cber/guidelines.htm.

REFERENCES

- 1 Blood Bank Transfusion Service Standards Program Unit. *Standards for Blood Banks and Transfusion Services*, 22nd edition. AABB: Bethesda, MD, 2003.
- 2 Orton SL, Virvos VJ, and Williams AE. Validation of Selected Donor-Screening Questions: Structure, Content, and Comprehension. *Transfusion* 40(11) 2000: 1407–1413. 🌐

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REFERENCES

- 1 Waeger R. The Future of Plasma Protein Therapies. Presented at *Plasma Forum 2003*, 11–13 June 2003 (Washington, DC). PPTA: www.pptaglobal.org.
- 2 Rankin PJ. Perilous Economics of the Industry. *The Source* (PPTA), September/November 2003: 5–10.
- 3 Turner P. Current Trends in the Plasma Therapeutics Industry. Presented at *International Plasma Protein Congress (IPPC) 2004*, 9–10 March 2004 (Brussels, Belgium). PPTA: www.pptaglobal.org.
- 4 Anderson NL, Anderson NG. The Human Plasma Proteome: History, Character and Diagnostic Prospects. *Mol. Cells Proteomics* 1(11) 2002: 845–867.
- 5 Over J. Plasma Protein Products, Opportunities for the Future. *Downstream PPB '03 Extended Reports*. Amersham Biosciences, 2004; [http://bioprocess.apbiotech.com/Applic/upp00738.nsf/4A6F5FFC1256E97003EF794/\\$file/18117706.pdf](http://bioprocess.apbiotech.com/Applic/upp00738.nsf/4A6F5FFC1256E97003EF794/$file/18117706.pdf).
- 6 Rankin PJ. Economics of the Plasma Products Industry. Presented at *International Plasma Protein Congress (IPPC)*, 9–10 March 2004 (Brussels, Belgium). PPTA: www.pptaglobal.org.
- 7 Christensen CM. *The Innovator's Dilemma*. Harper Business: Boston, MA, 1997.
- 8 Curling JM. Affinity Chromatography: From Textile Dyes to Synthetic Ligands By Design. *Intl. BioPharm* 17(7) 2004: 34–42; and *Intl. BioPharm* 17(8) 2004: 60–66.
- 9 *The World Health Report 2003: Shaping the Future*. World Health Organisation: Geneva, 2003; p. 30.
- 10 Robert P. Access to Therapy. Presented at *Plasma Forum 2002*, 11–12 June 2002, Arlington, VA. PPTA: www.pptaglobal.org
- 11 Robert P. Personal communication, The Marketing Research Bureau, August 2004.
- 12 *International Blood Plasma News*, April 2003, p 128. http://home.earthlink.net/~mrb_ibpn/home2.htm.
- 13 *Inventing a Better Future: A Strategy for Building Worldwide Capacities in Science and Technology*. InterAcademy Council, 2004; www.interacademycouncil.net/report can be accessed at www.interacademycouncil.net/Object.File/Master/6/720/0.pdf.
- 14 Boukef K, et al. *Transfusion Today*, December 1997. International Societies for Blood Transfusion.
- 15 Farrugia A. Plasma for Fractionation: Safety and Quality Issues. *Haemophilia* 10 2004: 334–340.
- 16 *Contract Fractionation: Facts and Figures*. Monograph Series No. 5, World Federation of Haemophilia, September 1998. Accessed at www.wfh.org
- 17 Gustafson M. Overview of Plasma Fractionation Practices. Presented at *FDA's Plasma Standards Workshop*, 31 August 2004; www.fda.gov/cber/summaries.htm#plasma. 🌐

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