SECTION 1

INTRODUCTION TO PLASMA FRACTIONATION

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THE HISTORY AND DEVELOPMENT OF THE PLASMA PROTEIN FRACTIONATION INDUSTRY

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1.1 THE EARLY HISTORY OF BLOOD TRANSFUSION AND BLOOD BANKING

The Latin term *serum*, for whey, was first used to describe "a watery animal fluid" in 1665. The word first entered the medical literature in the mid-nineteenth century to describe "the yellowish fluid of the blood that separates from a blood clot after coagulation" while *plasma*, the raw material for fractionation, was defined as the "liquid part of blood" . . . The provision of plasma for fractionation and the production of protein derivatives are historically linked to the development of blood transfusion and blood banking.

The modern era in blood transfusion is considered to have started with the work of James Blundell (1790–1877). His interest in transfusion stemmed from the involvement in cases of postpartum hemorrhage that he encountered as an obstetrician [1]. Following an extensive study of transfusion with dogs, he finally performed what is reported to be the first human blood transfusion with human blood on September 26, 1818. Blood was administered with a syringe device to a man with gastric carcinoma [2]. The man died of non-transfusion related causes. Blundell went on to perform a further 10 transfusions that included four successful treatments of postpartum hemorrhage [1]. He was a strong advocate of transfusion and hence served to advise in many other cases in London. One particular case had significant portent for the future. In 1840, a blood transfusion was performed on an 11-year-old boy to correct persistent postoperative bleeding-presumably caused by hemophilia A [3].

As experience with the fledgling technology increased, a review of blood transfusions performed by 1849 showed that 48 procedures had been carried out with mortalities in 18 cases, although the cause of death was not necessarily due to the transfusion. Transmission of air during the procedure was considered a major risk [4]. Clearly at this time many complications from hemolysis resulting from infusion of incompatible blood were not being recognized.

Transfusion remained a dangerous and unpredictable procedure up to the end of the nineteenth century. Attempts to improve transfusion generated further interest in the use of animal blood, until it was unequivocally proven to lead to intravascular hemolysis and hemoglobinuria [5]. Attempts were also made to use milk as a blood substitute, as it was believed that fat particles converted to red blood cells [6]. The impediment of coagulation on the ability to perform blood transfusion led to the use of sodium bicarbonate and sodium phosphate as anticoagulants or defibrinated blood [7,8]. But by 1880 the practice of blood transfusion had been essentially abandoned due to the unacceptable and unpredictable number of adverse reactions. This was advanced by the recognition that many cases of blood loss could be addressed by saline infusion [9].

The discovery of the A, B, O blood groups by Karl Landsteiner in 1901 was the key scientific discovery that would aid the identification and transfusion of compatible blood [10]. In 1902, the fourth blood type, AB, was also discovered by Decastello and Sturli [11]. Studies on cross-matching blood between donors and patients culminated in the first blood transfusion using blood typing and cross-matching by Ottenberg in 1907 [12].

However, as in the nineteenth century, the transfer of blood from donor to recipient remained a major technical hurdle, due largely to the clotting of the blood. The technique of direct transfusion by arteriovenous anastomosis was developed by

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Carrel in 1908 [13]. This procedure or a further modification, in which a bridging metal tube was used, allowed for practical if inconvenient transfer of blood. Eventually the procedure was replaced by a system developed by Unger in 1915 that removed the need for direct vessel anastomosis [14]. This system involved indirect transfer of blood using a double syringe and stop-cock apparatus.

Progress in the development of anticoagulants and the ability to store collected blood, coupled with an increasing appreciation of the need to ensure blood compatibility arising from the blood group discoveries of Landsteiner, were pivotal in making blood transfusion a practical and safe medical procedure [15]. Albert Hustin [16] initially reported the use of citrate as an anticoagulant in 1914 and it was further developed and applied by Agote [17] and Lewisohn [18,19]. Rous and Turner (1916) then developed a solution consisting of salt, isocitrate and glucose, which served as both an anticoagulant and a preservative of the red cells during refrigeration [20]. This timely development of a means of storing blood allowed the introduction of blood transfusion into the battlefield in World War I. The disadvantage of the Rous-Turner solution and its variants was that a high ratio of the solution to blood volume was required, hence diluting the collected blood. In 1943, an acid-citrate-dextrose (ACD) collection solution was developed by Loutit and Mollison, which could be used at a ratio of one part solution to six parts of collected blood [21]. Due to testing requirements the ACD solution was not accepted by the US Army until essentially the end of World War II in April 1945 [22].

The use of reusable rubber components and glass bottles to this point had been a source of inconvenience and provided inherent risks through contamination, clot formation, and air embolism. The development of a disposable plastic bag blood collection system by Walter and Murphy in 1952 addressed these issues [23]. The adaption by Gibson of a closed plastic bag system, not only to collect but also to separate blood components, was an important achievement contributing to the establishment of component therapy, thus enabling plasma collection [24].

The use of blood components rather than whole blood was considered a preferred option early in the history of transfusion medicine. According to observations made during the World War of 1914–1918, 80% of the mortalities on the battlefield were the result of blood loss rather than the direct effect of the projectile. In a letter to the *British Medical Journal* in March 1918, Gordon R. Ward advocated the use of blood plasma in battle instead of whole blood. Ward noted "A man apparently dying from haemorrhage is not dying from lack of haemoglobin, else severe cases of anaemia would die long before they do, but from draining away of fluid, resulting in devitalisation and low blood pressure" [25]. Its use would also serve to eliminate risks associated with whole-blood transfusion, in particular hemolysis through mismatched transfusion, and simplify the logistics of storing, transport, and administration. However, in preparing for war the British chose a different path, preferring whole-blood transfusions.

In 1914, Abel coined the term "plasmapheresis" to describe a process where blood was removed, the blood components separated and the cellular components returned to the donor. He had shown the feasibility of this procedure in dogs [26]. The first plasmapheresis procedure performed in humans was reported by Tui in 1944 [27]. This was followed by extensive studies by Grifols-Lucas in 1952 who reported findings on 320 procedures which involved removal of red cells by sedimentation or centrifugation from the collected blood and their reinfusion after as long as 1 week after collection [28]. The development of single use sterile plastic blood bags greatly increased the safety and convenience of the plasmapheresis procedure when compared to the previous situation involving reusable equipment [23,24]. However, the procedure remained too slow and labor intensive to serve as viable means of generating large volumes of plasma. The issue was resolved by the development of online blood cell separators.

The first blood cell separator, based on a dairy centrifuge, was developed by E.J. Cohn in 1951. It was further perfected by Tullis and consisted of a rapidly rotating conical vessel that separated cells from plasma [29]. The separated fractions could be harvested into separate bags and then retained or returned to the donor. The introduction of this machine made it feasible to utilize plasmapheresis as a means of collecting plasma for fractionation as well as in therapeutic apheresis [30]. Further development of the intermittent flow centrifugation to collect and separate blood components, was paralleled by the development of a continuous-flow centrifugation system that allowed the concomitant removal of plasma and the return of the remaining components to the donor [31,32]. Continuousflow centrifugation-based machines continue to be used in plasmapheresis to this day, especially in the collection of plasma for manufacture and for direct transfusion purposes such as the preparation of Fresh Frozen Plasma (FFP).

In parallel with the scientific developments, organizational structures were being established to cater for the provision of blood for medical use. The means to store of blood using the Rous-Turner solution enabled the establishment of the first blood depot in the field by the British under Oswald Robertson in 1916 [33]. In the 1920s Percy Oliver established a system of voluntary donor recruitment and assessment in London that was able to ensure a safe and reliable pool of compatible donors [34]. Following a visit to London, the Russian physician Alexander Bogdanov was motivated to establish a similar national transfusion infrastructure in the Soviet Union [35]. Until this time, collected blood was not being stored—blood donations and transfused soon after collection. In the Soviet Union, in the 1930s however, the procedure of storing blood and even shipping "canned blood" around the country was established by Yudin. The first facility that can be considered a blood bank was set up in Leningrad in 1932 [36]. In the Soviet Union during this time considerable use was made of cadaver-derived blood. A blood collection and transfusion service was also organized by the Republican Army during the Spanish Civil War (1936–1939), collecting 9000 L of blood [37]. In the United States, the concept of the "blood bank" was proposed and implemented by Bernard Fantus at the Cook County Hospital in Chicago in 1937 following observation of the Soviet experience [38].

With the onset of World War II blood procurement needed to be greatly expanded. The work of Charles Drew was a defining milestone in the establishments of the infrastructure and organization required for an operational blood service. Drew was responsible for the plasma for Britain program and established operational procedures to coordinate the activities of the American Red Cross (ARC) and the Blood Betterment Association in New York for the collection, processing, and shipment of blood components [39]. The provision of plasma for resuscitation of wartime casualties of the United States and British Armed Forces followed.

1.2 DEVELOPMENT OF SUBSTITUTES FOR TRANSFUSION

1.2.1 Lyophilized Plasma

After the First World War there was steady progress in fields related to the production and evaluation of plasma in the clinical setting so that by 1940 citrated plasma was the recommended treatment for shock. In 1940, confronted with the eventuality of war, the US Armed Services faced the problem of selecting appropriate blood substitutes and derivatives instead of whole blood. The National Research Council's (NRC) Subcommittee on Blood Substitutes chose dried plasma because of its "long preservation period, stability at extremes of temperature, its effectiveness as a replacement fluid, and the safety with which it can be administered" [40]. The US Army subsequently requested a supply of dried human plasma to treat combat casualties.

Emanating from an early observation by Paul Ehrlich on the stability of dessicated plasma, efforts had been made in the United States to develop technology for drying plasma and its clinical use had been investigated [41]. In 1940, however, there was still limited expertise in the industry. Robert Cutter, founder of Cutter Laboratories, noted in a later interview, that he had earlier considered investment in the food company—Birdseye, and that freeze-drying was more commonly used in the food industry for the preparation of, for example, dried coffee [42]. At the same time, Victor Grifols Lucas designed a lyophilizer to be used in the preparation of desiccated plasma and in 1943 received a US patent for this device [43].

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In 1941, the US Army made an agreement with the American Red Cross for the provision of human plasma that would be processed under contract by the pharmaceutical industry. Plasma was recovered by centrifugation and each donation was subjected to serological, bacteriological, and toxicity testing. The plasma was shell frozen in individual bottles and either stored or dried under vacuum. These products were controlled by the National Institutes of Health. The US Army awarded eight contracts for dried plasma. The first of these contracts for 15,000 250 cc units, was awarded on February 4, 1941 to Sharp & Dohme, because of their previous experience in the field. Subsequent contracts were awarded in 1941 to Eli Lilly and Co., Lederle Laboratories (Division of American Cyanamid Co.), Reichel Laboratories, Inc. (later the Reichel Division of Wyeth, Inc.), and in 1942 to Ben Venue Laboratories, Cutter Laboratories, Hyland Laboratories, and Parke, Davis and Co. [22]. Several of these companies were also involved in penicillin development and manufacture, as well as other products required in the war effort. Many chose to leave the blood processing industry at the end of the war when the supply of raw material was no longer assured.

In England, a small freeze-drying plant available in Cambridge was too small to meet the demand and a second unit was built by the Wellcome Foundation at Beckenham. With capacity to meet demand still inadequate, the Army Blood Transfusion Service built its own plant. During the last 2 years of the war, over 250,000, 400 mL bottles of freeze-dried plasma were produced [44]. Freeze-dried plasma was also made at the Lister Institute (which later became the Blood Products Laboratory (BPL)), for use by the Armed Forces and civilian establishments. A plant was also established in Scotland in 1941 with a government grant to the Scottish National Blood Transfusion Services (SNBTS) [45].

1.2.2 E.J. Cohn and the Development of Plasma Fractionation

The history of plasma fractionation is inextricably linked with the scientific and technological innovations of E.J. Cohn and his many coworkers at the Harvard Medical School. For a detailed description of his life and work the reader is referred to his biographer, Surgenor [46] who began his association with Cohn in 1943 and worked with him until Cohn's death in 1953. An historical analysis has been provided by Creager [47,48] and Cohn's work has been put in the context of the "story of blood" by Starr [49]. It must also be noted that Cohn himself wrote a history of fractionation in which he discussed the science and technology of fractionation, the characterization of plasma proteins and their clinical application [50].

Cohn's early work was dedicated to the introduction of protein chemistry at the Department of Physical Chemistry, which had been established at Harvard in 1920. This led to the association with Edsall [51] and later with Oncley, at the Massachusetts Institute of Technology, who was working on the dielectric properties of protein solutions, and later moved to Harvard. Shortly after the First World War, Cohn, then in his early 30s, traveled in Europe, particularly to Copenhagen and then to Sweden and England, where the foundation for his work on proteins was laid [52]. Cohn summarized the influences these visits had on his work in a much later publication in 1947 [53]. He had visited Theodore Svedberg's laboratory in Uppsala in 1926 and later acquired an ultracentrifuge for his laboratory. Also critical to his work on protein characterization and purity was the electrophoresis technique developed by Arne Tiselius also at the University of Uppsala. Cohn demonstrated both technologies at an American Chemical Society meeting in Boston in 1939. Early in 1940 Cohn had prepared two papers (first published in December that year), the first describing the separation of equine serum into successive fractions by the addition of ammonium sulfate across membranes and using controlled pH, ionic strength, and temperature [54]. The second paper described the separation of *bovine plasma* into five fractions [I, II, III, IV, and V] using ethanol-water mixtures added across membranes. Each fraction was obtained as a precipitate and the paper describes a procedure to obtain about 50 g of albumin from 2 L of plasma [55]. Its opening paragraph included the prescient statement "It has recently seemed of importance to standardize a method, capable of being employed for large-scale preparations, for the separation of plasma into as many as possible of its component proteins" [56].

One of the issues discussed at the first meeting of the Committee on Transfusions in May 1940, was the possibility of developing a substitute for human plasma. A report was considered from Dr. Owen H. Wangensteen from the University of Minnesota, on the possibility of administering bovine plasma to patients [57]. The committee decided to establish a program to investigate the use of bovine albumin as a plasma substitute. Cohn was engaged to manufacture and characterize a product for clinical evaluation [58]. A pilot plant, with a 40L batch capacity for optimization of fractionation procedures, was set up at Harvard in 1941. Armour Laboratories constructed a plant in Chicago to produce crystalline bovine albumin. Initial results were encouraging. Adverse reactions were thought by the investigators, including by Cohn, to reflect product impurity rather than immunological incompatibility. Particular emphasis was placed on producing a highly purified product by employing repeated crystallization. In what Surgenor called the "Norfolk Incident" a clinical trial was initiated using 200 men at the Norfolk Prison Colony. On September 14, 1942, 10 days into the trial, subjects started showing symptoms of serum sickness and the trial was stopped. Tests were developed that it was hoped would identify albumin batches that would not cause adverse reactions. This was not successful and administration of such a screened batch also resulted in a serious reaction. This was the last attempt and the program to develop bovine albumin for clinical use was formally ended on March 23, 1943.

The focus shifted to the production of human albumin that had been in development in parallel [59]. The US Navy spoke for all the Armed Services when it stated that what was required was a "safe, stable, compact blood derivative, immediately available without reconstitution for emergency use, for the treatment of shock and burns" [60].

The first fractionation of human plasma had been carried out by Armstrong at the Harvard laboratory in August 1940 [60] but by the first half of 1941, the human albumin produced was only available on laboratory scale. The first lot of albumin from the pilot plant was released for clinical use as 100 mL bottles of 25% solution on July 9, 1941. By mid-September over 3 kg of albumin had been prepared and Cohn recommended that Armour be contracted to fractionate human plasma in order to fulfill expected needs. Work had continued on the fractionation methods: the precipitation of Fractions II + III had been combined and Fraction IV had been split into two fractions, IV-1 and IV-4 (Method 6) to obtain as many products as possible. Cohn was prohibited from publishing his work until 1943-1944 and by agreement with the Journal of Clinical Investigation published an entire volume of 23 papers from the Harvard group [61]. However, only one paper carried Cohn's name. It is the 1946 American Chemical Society publication describing Method 6 that is generally cited as the original reference [62].

The first use of Cohn's human albumin preparation for the treatment of traumatic shock was by Charles Janeway at the Brigham Hospital in April and May 1941. D.B. Kendrick of the US Army reported: "This patient was 20 years of age and was admitted to the hospital 16 h after injury. He had a bilateral compound continued fracture of the tibia and fibula. He had fractures of five ribs with associated pleural damage, pneumothorax and subcutaneous emphysema. At the time of admission, his blood pressure was 76/30. Two bottles of albumin, consisting of approximately 25 g, were injected over 30 min. The blood pressure after injection was 106/70 . . . his blood pressure remained above 130 . . . he has had no evidence of circulatory failure since the albumin was administered . . . this patient appeared quite groggy and irrational when I first saw him, but 12 hours later he was very clear mentally and appeared to be feeling better" [63].

Initial treatment of casualties from the attack on Pearl Harbor on December 7, 1941 was with dried human plasma. Isador Ravdin, Professor of Surgery at the University of Pennsylvania was flown to Hawaii to manage the treatment of casualties taking with him all the available vials of human albumin from the Harvard pilot plant. Ravdin reported 10 days later: "All seven patients were given albumin, and all showed prompt clinical improvement, including one whose state was so critical that the administration of albumin to him was debatable. There was no question as to his response: He was unconscious in the morning when he was given 250 g of albumin. In the afternoon, he was talking, but was disoriented. The following morning, he was given the same amount of albumin. Twenty-four hours later, the edema had disappeared and he was taking food by mouth." Human albumin was recommended for official clinical use to the Surgeons General of the Army and Navy by members of the NRC Conference on Albumin on January 5, 1942 [64,65].

Cohn and his Harvard colleagues' work were by no means restricted to the purification of albumin. Oncley, supported by immunologists J.F. Enders and W.C. Boyd, investigated the purification of immunoglobulin from Fraction II + III and his frequently cited paper presenting Method 9 for the purification of immunoglobulins and other plasma proteins was published in 1949 [66]. In concert with the Harvard effort, H.F. Deutsch at the University of Wisconsin was also investigating subfractionation methods for the recovery of IgG from Fraction II + III. In 1946, he reported a method that increased the recovery of IgG from 50% to 75–80% and later that year, working with pastes from Armour and Cutter, he described a method that enabled a 95% recovery [67,68]. He also investigated pepsin digestion to enhance recovery of immunoglobulins from ethanol-plasma precipitates [69].

The first indication of the importance of antibody concentrates in treating disease occurred during a measles epidemic in Philadelphia in the winter and late spring of 1942–1943. Joseph Stokes found that administration of a solution of Fraction II + III to infants prevented the disease [70]. At this time a paper by Enders and others, characterized the antibodies present in Fraction II + III accounting for its biological properties and showed that the antibodies could be classified as neutralizing, complement fixing, agglutinating, and protective [71].

As result of Stokes's work, human immune serum globulin was recommended to the Armed Forces on March 22, 1943. In 1944, the American Red Cross, in cooperation with manufacturers, instituted a program to make surplus immune serum globulin for prevention of measles available to the American people at cost. This initiative marked an important departure into providing plasma products for civilian use [72, 73]. By 1945, the production and characterization of immunoglobulin preparations was well established. Janeway noted that immunoglobulin was being made from pools of 2000 to 6000 donors, that the antibody spectrum varied with viral epidemics, such as influenza A, that the purity of preparations had been increased to 98% and that glycine was an important stabilizer [74]. Cohn himself, in addition to continuing to develop the process for the purification of immunoglobulins, undertook studies to characterize the antibody constituents of Fraction II+III specifically describing the "blood-typing globulins"-the

anti-A and anti-B isoagglutinins—and the anti-Rh antibodies of Fraction II + III [75].

In addition to the purification, properties and use of albumin and immunoglobulins, Cohn had a considerable interest in the clotting-related proteins. In his own history of fractionation, he has a significant section on clotting factors and describes fibrinogen and the structure of the fibrin clot, prothrombin and thrombin, antithrombin, and plasmin. Surgenor mentions that although Cohn never saw a patient himself, he was always concerned with the clinical use of the products of fractionation. Consequently, Cohn's own paper contains a summary of work on the use of Fraction I in the treatment of hemophilia, fibrin foam and thrombin in hemostasis (which involved Isador Ravdin, who had administered albumin at Pearl Harbour), fibrinogen and thrombin in skin grafting, fibrinogen and thrombin in burns, and fibrin film as a dural substitute [75].

Cohn, understanding that the previously published methods had been developed under wartime stress, continued to research ethanol-based precipitation methods. He published Method 10 in 1950, 3 years before his death. Cohn notes: "Method 10 of plasma fractionation has been designed to be equally applicable on any scale from a few milliliters to thousands of liters of plasma" [76]. In an extensive review, John T. Edsall, Cohn's long-time colleague at the Harvard Medical School published the underlying physical chemistry of Cohn's methods [77]. In the midst of the development of fractionation procedures and despite the war years, Cohn and Edsall had also published their seminal work on protein chemistry [78]. Summing up his work in an article in Science, Cohn concluded with "The control of infectious diseases by passive immunization with γ -globulins may well be the largest need of a civilian population for a blood derivative . . . and . . . We must continue, as we have begun, to make available as many as possible of its diverse cellular, protein and lipid components, separated and concentrated as specific therapeutic agents, of value in different conditions, in the interests of the most effective and economical use by a society of the blood which it contributes" (Figure 1.1) [79].

1.3 THE ESTABLISHMENT AND DEVELOPMENT OF THE PLASMA FRACTIONATION INDUSTRY IN NORTH AMERICA

At the meeting of the NRC in January 1942, Armour Laboratories and Lederle Laboratories were considered capable of producing plasma-derived proteins provided technicians were trained for a month at Cohn's laboratory. In all, seven contracts were eventually drawn up with Armour, Lederle, Upjohn Co., Eli Lilly Laboratories, E.R. Squibb, Cutter Laboratories, and Sharp and Dohme. These companies became the first commercial fractionators. Some



FIGURE 1.1 E.J. Cohn's illustration, from 1944 to 1945, of the main fractions of plasma and their therapeutic value. From Ref. [79]. This article was originally an Address delivered on 11 December 1944 at the ceremony of the Award to the National Research Council by the American Pharmaceutical Manufacturers Association, NY. Reprinted with permission from AAAS.

were also involved in the production of freeze-dried plasma. Most of these companies (except Armour and Cutter Laboratories) were wary of the continuing availability of plasma for fractionation in peacetime and left the business on the expiry of their 1941 contracts. Robert Cutter notes "... when you'd take the military out of it, the demand for these products among civilian medical profession would not be sufficient to maintain the very expensive process of round-the-clock preparation. And getting the commercial blood ... is a very important problem of supply, a very difficult problem" [80].

In fact in the immediate post-war years the ARC, which had collected 13.3 million pints of blood during the war and shipped 300,000 tons of supplies abroad, closed its blood centers. As a result, placental blood was considered an alternative source and Cohn's methods were adapted to placental extracts by researchers at the Laboratory Division of the Michigan Department of Health. Methods were described to extract and purify albumin [81] and immunoglobulins [82] and adopted by several manufacturers. As in the Soviet Union, the possibility of using cadaver blood was considered as a potential source but was rejected on ethical grounds and the fact that it would not satisfy the volumes of plasma required [83]. With growing demand, however, and the onset of the Cold War, plasma derivatives, together with blood and blood components, were increasingly seen as a necessary strategic resource, in case of war or catastrophe. In response, plasma collection was expanded in the United States in the late 1950s through the use of plasmapheresis and the recruitment of remunerated donors by commercial processors. The involvement of the ARC in blood collection recommenced when it opened its first center in Rochester, NY in January 1948. The American Red Cross continued to increase its capacity to collect large volumes of primarily outdated recovered plasma from volunteer donors.

The American Association of Blood Banks (AABB) was formed in 1947 and represented the independent collection centers outside the ARC [84]. The AABB mission was to "promote common goals among blood banking facilities and the American blood donating public" [85]. The early American fractionators were dependent on paid donors or agreement with the American Red Cross that voluntary donated blood could be used for the commercial production of plasma derivatives.

As mentioned earlier, most companies involved in the processing of plasma during the war left the business on the expiry of their contracts, principally due to concerns about the ongoing availability of plasma and the viability of the industry without a strong military need. However, several companies persisted and made a significant contribution to the development of a sector that has delivered considerable health benefits.

Cutter Laboratories, founded in 1897, had by 1938, started making infusion solutions at their California plant. Cutter began plasma fractionation in 1942, thereby becoming the first commercial producer of albumin. Cutter completed its Clayton, North Carolina facility in 1974 and was acquired by Bayer AG the same year. Soon after, it was merged with Miles Laboratories.

Armour & Company, the largest supplier of albumin to the US military during WWII, constructed a plant in 1943 under a US Navy contract at Fort Worth, Texas, because of proximity to a large donor population [86]. Plasma was obtained from American Red Cross centers processing about 3000 donors per week, equivalent to about 600 L of plasma per week. As an illustration of early plasma supply problems, the plant temporarily stopped operations at the end of the war. Industrial manufacturing issues such as the provision of pyrogen-free water and reagents, heavy metal contamination, ensuring adequate solution mixing, involving a change from dialysis to capillary jet addition into tanks with impellers were identified and resolved. A new fractionation plant was established in Kankakee. Illinois in 1953. Armour was taken over by Revlon in 1977, acquired by Rorer Pharmaceutical in 1986 and merged with Rhône-Poulenc in 1990.

Baxter was founded in 1931 and was the first company to make intravenous solutions for hospital use. In 1939, Baxter

introduced the first sterile vacuum-type blood collection unit, allowing the storage of blood for up to 21 days and therefore making blood banking practical. Later, in 1941, Baxter introduced a plasma vacuum container enabling the storage of plasma for future use. In 1952, Baxter acquired Hyland Laboratories, which during the war had been involved in the production of freeze-dried plasma and in 1953 built a 177,000 ft² facility in Los Angeles, California, to begin producing hyperimmune globulin, albumin, and a variety of blood bank, coagulation, and biochemical test products.

Courtland Laboratories, founded in 1947, was granted a license to manufacture blood plasma products in 1950. The company had a diverse product line including bovine albumin manufactured for Max Factor cosmetics and rabbit serum for Merck Sharpe & Dohme. They also produced freeze-dried and liquid human plasma and later began fractionating plasma [87]. Courtland was acquired by Abbott Scientific Products, a division of Abbott Laboratories in 1967 and was subsequently sold to the Green Cross Corporation in Japan in 1978, being renamed the Alpha Therapeutic Corporation.

In 1969, the New York Blood Center (NYBC), then called the Community Blood Council of Greater New York became the first American blood transfusion service to be licensed to fractionate plasma. The Center produced the first low cost, plasma-derived hepatitis B vaccine in 1978 and completed financing of its Melville Laboratories on Long Island in 1979. The new fractionation facility opened in 1980 with an annual capacity of 300,000 L and an agreement with the ARC to manufacture plasma derivatives [88]. Shortly after A.M. Prince and B. Horowitz started development work on viral inactivation of blood components and plasma derivatives, leading to the introduction of solvent/detergent (S/D) technology [89]. S/D-treated coagulation factor concentrates were first licensed in the United States in 1985. V.I. Technologies (Vitex) was founded in 1995 as a for-profit spinout from the NYBC and the first product, an S/D-treated plasma (PLAS + SD) was licensed in 1998. PLAS + SD was manufactured by Vitex from a maximum of 2500 ABO donor pools at the Melville facility and distributed by the ARC. Following fatal adverse events in 2002, product was withdrawn in the United States.

The Massachusetts Biologic Laboratories (MBL), formerly the Massachusetts Public Health Biologic Laboratories, was the only non-profit, FDA-licensed manufacturer of vaccines and other biological products in the United States. The laboratory was established in 1894 with the first diphtheria antitoxin (antibody) being produced in 1918 in response to a severe epidemic that occurred in the early 1900s [90]. Fractionation of plasma recovered from outdated blood collected by the ARC in Massachusetts was begun in 1946 [91]. MBL had been a part of the University of Massachusetts Medical School since 1997 but the 150,000 L fractionation unit, which focused on hyperimmune products, ceased operation in 2006. The ARC also moved to establish its own fractionation capability in 1978 by negotiating an agreement with Baxter to construct a US\$ 45 million plant with a 1 million L capacity. However, the proposed joint-venture ran into legal, commercial, and jurisdictional issues and the agreement was terminated a year later. Instead, the ARC contracted Baxter to fractionate the ARC plasma into products that were then sold and distributed under the American Red Cross label. This arrangement formalized the reconciliation between pharmaceutical production and voluntary or altruistic blood and plasma donation. The contract manufacturing agreement was terminated in 2005 when the ARC chose to exit the plasma derivatives business and was replaced by a long-term plasma supply agreement with Baxter.

Activities to establish a fractionation facility in Canada were also occurring. Connaught Laboratories, known for pioneering work on insulin production, was founded in 1913 and incorporated by the University of Toronto in 1914 with a remit to provide biological products to the Canadian public at reasonable cost. Entry into the plasma fractionation industry occurred as a consequence of the extensive work conducted by Charles Best on heparin [92]. In 1972, the University sold Connaught to the Canadian Development Corporation and then in 1989, the facility was sold to Institut Mérieux. Plasma fractionation was carried out, primarily with plasma supplied by the Canadian Red Cross, between 1953 and 1987. In the mid-1970s the Ministry of Health proposed that Connaught construct two new plants, one in Winnipeg and one in French Canada at the Institut Armand Frappier in order for Canada to become self-sufficient in the manufacture of plasma products. The Winnipeg facility was built and the Canadian Red Cross was extensively involved between 1975 and 1990, in defining a business model to justify plasma fractionation in Canada. All were refused by the Canadian government and in the end Canada was left without a national fractionator [93].

However, a world class capability for the production of specialist hyperimmune products was developed at the Winninpeg site, by the Rh Institute, established by the University of Manitoba in 1969 as a private, non-profit organization to undertake research into hemolytic disease of the fetus and newborn (HDFN). The focus of the new institute became the isolation of anti-D immune globulin from women naturally immunized with Rh positive red cells for prevention of HDFN. Anion exchange technology for the isolation of immunoglobulins was adopted from H. Hoppe's laboratory at the Central Institute for Blood Transfusion in Hamburg [94]. An intravenous product was approved for clinical evaluation in 1977 and for use by Health Canada in 1980. The chromatographic manufacturing capability of the facility was developed by 1983 to include albumin and immunoglobulins to a capacity 75,000 L per year and constituted the first, fully automated industrial scale chromatographic plant in North America. The inability of the Canadian Red Cross and the

Canadian government to agree on a funding model for plasma fractionation resulted in the facility never becoming a commercial producer of albumin and immunoglobulin.

The Institute became Rh Pharmaceuticals Inc., a private, for-profit company in 1990, and amalgamated with Cangene in 1995 [95]. Today Cangene is the world's leading manufacturer of hyperimmune products including biodefencerelated hyperimmunes, and operates four plasma collection centers in the United States. In June 2010, the company announced that it was developing an IVIG product, which is currently in the preclinical research phase.

1.4 THE PLASMA FRACTIONATION INDUSTRY IN EUROPE

1.4.1 Establishment and the Pioneers

After the fall of France and the collapse of the "Blood for France" program the American Red Cross turned its effort in supporting eight New York hospitals contributing to the "Plasma for Great Britain Project." This program was conducted by The New York Blood Transfusion Betterment Association headed by Charles Drew [39]. As has been mentioned Drew was an exceptional individual who made significant contributions, both scientifically and in terms of policy, to the provision of plasma for emergency use and fractionation. Not only had he introduced centrifugation for separating the plasma and cellular components of blood, first used in Britain but, as an African American, had battled the existing segregation of blood from different racial groups to segregated recipients.

On leaving the Plasma for Britain program, Drew was quoted as saying: "The disservice that has been done, has been done not only to the Negro people but to the cause of truth itself. How have we, in this age and in this hour, allowed once again to creep into our hearts the dark myths and wretched superstitions of the past . . . In the laboratory I have found that you and I share a common blood; but will we ever, ever share a common brotherhood? As repugnant as this scientific fact may appear to some, their quarrel is not with me, but with the Giver of Life whose wisdom made it so" [39].

The work of Drew and the American Red Cross to provide blood to Europe, exposed European authorities to policies, practices and technology that would be used to establish or improve the local blood collection capability and would subsequently underpin the development of a local fractionation capacity. However, the path that it took was quite different. Whereas in the United States, plasma fractionation was seen as predominantly a commercial enterprise, in Europe with its diversity of traditions and cultures, fractionation became divided into two sectors commercial and not-for-profit sectors, with the latter frequently under the auspices of the various national Red Cross societies. A brief overview of the major entities involved in establishing the European fractionation industry is presented below.

In Germany and France both commercial and not-forprofit fractionators coexisted. Behringwerke AG in Germany had been founded by Emil von Behring in 1904 to produce sera and vaccines to combat infectious diseases. Behring had earlier in 1901 received the first Nobel Prize in Physiology or Medicine for his work on diphtheria and tetanus immunization. The company had developed freeze-drying technology for other biological products and was in a strong position to commence plasma fractionation. After the Second World War, in May 1945, the company, operating under the control of the United States Authorities, started its first fractionation activities with freeze-dried plasma inventories given to the company by the US Army [96]. Later the company sourced plasma from remunerated donors in Germany, Austria, and elsewhere in Europe. The company introduced a 20% albumin and an intramuscular immunoglobulin product in 1949 setting a course for the continuous development of a full range of plasma-derived products [97].

Biotest AG has a similarly long history, starting in 1860 with the production of photographic (X-ray) plates for Röntgen. The Biotest Serum Institute GmbH was incorporated in 1946, initially focusing on blood group serology. It introduced a gelatin plasma expander in 1957 and a 5%, standardized, stable, virus-inactivated (β -propriolactone/UV irradiated) plasma protein solution containing primarily albumin (3.1%) and immunoglobulin (0.7%), in 1968. An extensive range of plasma products was subsequently developed and marketed.

In Spain F. Duran-Jordà created the first transfusion service in Barcelona 1936 for the Republican Army Health Service. Duran-Jordá produced small 300 cc aliquots of "standardized" filtered blood under sterile conditions. These units were derived from six donations to minimize ABO titers of isoagglutinins [98]. Donors were encouraged by the prospect of receiving food in one of the first voluntary, nonpaid but rewarded donor organizations. Concurrently, J.A. Grifols Roig had designed the "Flébula," a 500 cc vacuum container containing anticoagulant for collection and infusion. Recognizing the medical and commercial opportunities at the end of the civil war to address developing transfusion requirements, J.A. Grifols Roig and his two sons, all of whom were physicians, opted out of medical practice to incorporate Laboratorios Grifols in November 1940. Building on the work of Duran-Jordá, Grifols introduced single donor, lyophilized plasma in 1943 and opened the first private blood bank in 1945 at the Instituto Central de Análisis. This became the company premises and is now the Grifols Museum. In 1952, J.A. Grifols Lucas described a procedure for the return of red blood cells to the donor leading to the development of plasmapheresis and paving the way for commercial fractionation in Spain [28].

Institut Mérieux was created in France in 1897 to manufacture sera and vaccines and developed a core competence in passive and active immunization. The company introduced a formalin-stabilized human serum in 1942 and started production of human plasma derivatives from placenta in 1952. Mérieux collected placenta from 7500 maternity centers around the world, a contribution equivalent to 1 million L to the plasma supply [99]. The fractionation unit close to Lyon introduced ion exchange chromatographic fractionation technology using dextran-coated, beaded silica for the manufacture of albumin in 1980 [100]. Institut Mérieux became Pasteur Mérieux Serums and Vaccines, a subsidiary of Rhône-Poulenc, and finally stopped albumin manufacture from placenta in 1993 in response to a directive from the French Minister of Health because of vCJD safety concerns. However, the company continued to produce βglucocerebrosidase, the unmodified enzyme used as the basis for Ceredase[®], marketed by Genzyme Corp. [101]. Behringwerke, Berna in Italy, Kabi in Sweden, and Green Cross in Japan also fractionated placental serum and the Serum Institute of India installed a plant to manufacture placental albumin in 1985 [102]. Behringwerke (later Centeon and now part of the CSL Group) produced a Factor XIII concentrate from placenta from the 1970s until 1992 [103].

1.4.2 Red Cross and Government, Not-For-Profit Fractionation in Europe

In Britain, the Lister Institute, founded in 1891, formed a starting point for not-for-profit fractionation. The Institute had moved from London to the country village of Elstree to be able to develop vaccines and antitoxins in animals. The Blood Products Laboratory, BPL, a continuation of the Biophysics Division, was established at this site in 1948. It was dependent on the National Blood Transfusion Service, which had been established at the end of the war, to provide blood plasma for fractionation [104]. A smaller Fractionation Laboratory in Oxford was adsorbed into BPL in 1992. Although now incorporated as Bio Products Laboratory Ltd., BPL remains a government owned institution.

In 1941, the British government considered that the output of freeze-dried plasma from BPL would be inadequate for military requirements and decided to establish a facility in Scotland. The Protein Fractionation Center of the SNBTS was opened in 1950. It ceased operations in 2008, in part due to the necessity to import "commercial" plasma as a consequence of the vCJD outbreak in Britain [105]. The SNBTS is most well known for the development of the continuous small volume mixing (CSVM) process—an early development of continuous biological product processing developed by J.G. Watt and P.R. Foster [106] and also reported from Cutter Laboratories [107].

The French history of not-for-profit fractionation has its roots in the creation of the Transfusion Sanguine d'Urgence

(TSU) by Arnault Tzanck and others in Paris in 1928. This service, which later became the Centre National de Transfusion Sanguine (CNTS) in 1949 cooperated with the French government through the Assistance Publique [108]. Voluntary and benevolent blood donation was regulated by French law from 1952 and although modified in subsequent years, the principles of this law still govern transfusion practice in France today. In addition, a law from 1901 prohibited the generation of profit from blood products [109]. As in many countries this generated a conflict when commercial plasma products were made from voluntary donations. The response varied on a case-by-case basis exhibiting responses ranging from slavish observance of regulations to pragmatism.

Plasma fractionation, based on Cohn's methods, was a logical continuation of the transfusion service. Regional fractionation centers were created in Montpellier, Bordeaux, Lille, Lyon Strasbourg, and Nancy, each with accompanying research laboratories. At the CNTS in Paris efforts were made to apply the antiseptic Rivanol[®] (ethacridine lactate) to precipitation of plasma proteins [110].

In other countries of Europe, the Red Cross established voluntary blood donation/transfusion centers and plasma fractionation was established as an extension of the transfusion service. The Finnish Red Cross Blood Transfusion Service was established in 1948 and fractionation of 2000–3000 L of Finnish plasma per year started at the State Serum Institute in 1950 with equipment donated by the American Red Cross. As larger quantities of Finnish plasma became available in the 1960s fractionation was contracted to the Netherlands Red Cross, to the Swiss Red Cross, and to Kabi in Sweden. In 1972, a new 60,000 L plant was commissioned in Helsinki and Finland again became self-sufficient in plasma products [111] but this facility was closed in 2004.

In Sweden, Kabi had its origins in the brewing industry but in 1941 was contracted to make lyophilized plasma. At the end of the war it had a surplus inventory of plasma that was used for fractionation. Once established, Kabi become the national fractionator of plasma from the Swedish regional transfusion services, using plasma collected from remunerated donors [112]. With close links to Pharmacia, the company was an early adopter of chromatographic technology in fractionation. Kabi also made a 5% sterile ceruloplasmin product that was given to a limited number of schizophrenia patients [113].

Red Cross transfusion services were also critical in a number of other countries in establishing collection centers and promoting the establishment of fractionation facilities. In the Netherlands, a blood collection and transfusion service was established in 1930 and the capability to produce lyophilized plasma was available by 1940. Fractionation was established soon after the war at the Central Laboratory of the Netherlands Red Cross [114]. In Switzerland, civilian transfusion services, run by the Red Cross, were established in 1949 and the ZLB (Zentrallaboratorium, Blutspendedienst SRK) was formed later that year. In 1951, the Swiss Federal government mandated that Switzerland become selfsufficient for the supply of blood. ZLB's first production plan for plasma products was made in 1954. In that year P. Kistler at ZLB's pilot plant and H. Nitschmann, Professor of Biochemistry at the University of Bern, published their modifications to Cohn's Method 10 [115]. Ongoing development of the Kistler-Nitschmann technology resulted in the publication in 1962 of a method with improved yields and purity as well as reduced alcohol requirements [116]. Two German Red Cross (DRK) centers, in Springe and Hagen, also embarked on fractionation. However, the DRK centers lost their tax-exempt status in 1971 because the manufacture and sale of their plasma products was deemed to be profitable [117]. Hagen became known for its alternative methods of fractionation including a heat-ethanol method to isolate albumin with the concomitant denaturation of IgG [118]. The Springe facility continued to operate and was eventually purchased by Octapharma AG in 1999.

In Italy after the First World War, a few Italian hospitals were able to provide blood transfusions from paid donors. As a result of the initiative of the Milanese physician Davide Formentano, voluntary donation was introduced in 1927 and led to the foundation of the Italian Voluntary Blood Association (AVIS). Forty years later Italy enacted the first law placing the blood services under state control. The Italian blood system reform Act 107 of 1990 reaffirmed voluntary donation and placed national policy and self-sufficiency under the Health Ministry. In the wake of the HIV and hepatitis C infections through transfusion in the 1980s it was determined that safety was to be achieved by the fractionation of Italian plasma at only two locations in Italy. This prevented international companies such as Baxter, Immuno, Biotest, and Behring from fractionating Italian plasma and restricted fractionation to Sclavo and Farmabiagini [119]. In 1995, the "Blood Derivatives Production Centers" Act mandated that two fractionation facilities be established, thus laying the legal foundation for the Marcucci (now Kedrion) Group's two fractionation plants in Italy [120]. Act 219 was introduced in 2005, promoting self-sufficiency but allowing European Union-based companies to operate within the market.

In Russia there are approximately 2 million blood donors of whom 91% are voluntary. Thirty percent of plasma for fractionation is collected by plasmapheresis and 96% of blood donations are used as components. In 2009, just over 1 million L of plasma were collected, 1.8% rejected and 51% used for fractionation. Since 1989 the production of both albumin and immunoglobulins has declined significantly in the wake of uncertain political stability [121]. The aggregate fractionation plant capacity of the Blood Transfusion Services is reported to be 300,000 L but only 180,000 L were fractionated in 2008. In addition, there are five small centers with capacities of about 30,000 L each [122].

In 1970, Richard Titmuss, an advisor to the UK Labour government, published his controversial text "The Gift Relationship: from human blood to social policy" [123]. By examining blood collection data and contrasting the approaches used in the United Kingdom and the United States, Titmuss argued that altruistic, voluntary donation leads to a safer supply and less wastage in the blood collection system. This theme was also explored by Hagen in "Blood: gift or merchandise" published a decade later, which documents the state of the plasma processing industry in 1982 and the complex issues surrounding plasma supply on a more global basis [124].

In retrospect, Titmuss's book can be seen as a critical point in defining the direction taken by the European fractionation industry through the influence on the adopted plasma collection options and the resultant impact on plasma availability and hence the fractionation capacity that could be developed.

Titmuss argued that the frequency of hepatitis B antigen (HBsAg) in blood donor populations, and therefore the challenge this viral infection may have presented to the safety of plasma products, was under scrutiny. In the United States, the rate of hepatitis B infection was estimated to be 0.1-0.5% in voluntary donors and 1-2% in paid donors. Significantly higher differentials were seen elsewhere [125]. A later review summarizes data from the 1970s and notes that the estimated carrier rate for paid donors was 6.3%, while that for volunteer donors was less than 0.6% [126]. However, Domen concluded that not all commercial blood donors were associated with a higher risk of transmission of hepatitis [127]. The multiple contributions to improve safety of the supply were summarized by Tobler and Busch [128] and the status in 2004 has been reviewed by Farrugia [129].

The debate, which continued in the Journal of Medical Ethics into the late 1990s, contributed to a focus in developing voluntary, non-remunerated sources of plasma in Europe [130-132]. The European Directive 89/381 requires the member states of the European Union to take "all necessary measures to promote Community self-sufficiency in human plasma" and to "encourage the voluntary unpaid donation of blood and plasma" [133]. Interpretation of the directive is given by P.J. Hagen in a European "white paper." Hagen also relates the divergent opinions between the commercial and some not-for-profit protagonists [134]. On a global basis the World Health Assembly in 1975 urged countries to "promote . . . voluntary, non-remunerated blood donation" Furthermore, "all countries should strive for self-reliance at least for the supply of major blood products" [135]. With few exceptions, notably, Germany and Austria, plasma for fractionation in Europe has been derived from voluntary donors of both blood and plasma.

1.4.3 For-Profit Fractionation in Europe

Despite the highly regulated access to plasma in the European environment two commercial plasma fractionation

companies were established without any ties to national blood collection agencies. Immuno AG, formed in 1953, commenced plasma fractionation in Vienna in 1954 and was the first company in Europe to introduce widespread plasmapheresis centers in both Austria and Germany, opening the first center in 1960 [136]. The company quickly became one of the leading fractionators in Europe and acquired an old fractionation plant from Parke-Davis in New York State as well as plasma collection centers to assure plasma supply from the United States. Immuno was merged into Baxter Bioscience in 1997.

Another, privately owned company, Octapharma, was established in Vienna in 1983. As the name implies initial focus was on Factor VIII products with the first commercial solvent–detergent treated Factor VIII concentrate approved in 1986. Octapharma acquired its manufacturing facility in Vienna in 1989 and initiated an aggressive expansion plan throughout the following decade [137]. The company has also pursued a contract manufacturing strategy, mostly for non-profit organizations. Clients include services in Germany, Israel, Norway, Slovenia, and Poland [138]. The Norwegian project in particular has been reported to be very successful [139].

1.5 NATIONAL POLICIES AND SELF-SUFFICIENCY

Self-sufficiency policies and national needs together with technical opportunities for both small- and large-scale fractionation led to a proliferation of the industry in the 1970s and 1980s. By 1984, the first year in which the Marketing Research Bureau conducted a worldwide survey, there were 95 plasma fractionators with a total capacity of 15 million L, fractionating some 12 million L. Sixtysix percent of the plants were in Europe and 11% in North America but 43% of the capacity was in Europe and 45% in North America. In 1990, there were 102 facilities, 56 in Europe, and 10 in North America. European plant capacity had grown to almost 11 million L with close to 8 million L capacity in North America. Japan and Asia (mainly Australia) had a capacity of 2.6 million L with the rest of the world accounting for only 1 million L. By 1993 more than 40 plants had a throughput of less than 50,000 L [140]. Many of these plants were located in Eastern European countries, some countries in Asia and one in South Africa. Establishment of small-scale fractionation was enabled, in part, by the introduction of chromatographic technology [141] for instance in Johannesburg, Budapest, and Skopje (Macedonia), although the issue of small-scale pharmaceutical fill-finish was unsolved [142]. The debate on small-scale fractionation continued until the end of the century. J.K. Smith held that "the initial costs are daunting, there may be difficulty in recruiting well-trained nationals to key posts" and argued that high priority be given to the development of the regulatory agency [143]. J.G. Watt's analysis stressed the necessity of stringency from feasibility to commissioning, the importance of GMP and noted that "The technology of fractionation . . . is quite simple but the application of and the development of good housekeeping practices, about 85% of the task, is very hard to establish" [144]. J. Leikola pointed out that plant size is not always an indicator of feasibility since the Finnish Red Cross was breaking even fractionating 100,000 L whereas as Kabi was making a loss at 250,000 L annual throughput [145]. R. Herrington at CSL asked "why a national government or private investor would want to invest some US\$ 200 million to build a national plasma fractionation plant" and considered that the "entry level costs are far too high compared to alternative options." These options were contract fractionation arrangements in one form or another [146].

An interesting case study of the path to achieve selfsufficiency is provided by the experience of Brazil. Immuno built a plasma fractionation plant in Brazil in the 1970s. This plant was subsequently purchased by Behringwerke, then a subsidiary of the German chemical giant Hoechst. Hoechst announced in 1991 that it was closing the fractionation plant, leaving Brazil without an adequate, national supply of plasma products. In response to this the Ministry of Health announced plans to build fractionation facilities in São Paulo and Rio de Janeiro using largely chromatographic technology from the Centre Régional de Transfusion Sanguine in Lille. By 1996 plasma product imports into Brazil had risen to about US\$ 100 million per annum and, due to the closure of the Foundation Santa Catarina plant, these original plans were amended to envisage the construction of three new plants. Further discussions on self-sufficiency in 1998 led to a proposal for a US\$ 140-170 million facility and later to the potential private sector involvement with Biobrás. Currently, there is a national self-sufficiency plan with Hemobrás, formed in 2006, and supported by the Brazilian Ministry of Health, to construct a 500,000 L fractionation plant in the state of Pernambuco [147] with technology from LFB SA in France, as LFB currently toll manufactures products from Brazilian plasma [148]. A smaller facility with a capacity of 150,000 L is also under construction at the Instituto Butantan in São Paulo under the auspices of the Secretariat of Health of São Paulo State and Fundação Butantan [149].

Further afield in South Africa, self-sufficiency in plasma products was also being pursued. Blood collection in South Africa commenced in the 1930s and the main center, the South African Blood Transfusion Service (SABTS) was named in 1943. Regional services declined establishment of a national service and the Durban center formed the Natal Blood Transfusion Service (NBTS) in 1959 [150]. The Plasma Fractionation Division of the NBTS was established in Pinetown in the 1970s. Now known as the National Bioproducts Institute (NBI) to reflect the national mandate, the laboratory fractionates about 150,000 L of recovered plasma annually using Cohn and Kistler–Nitschmann technology. In Johannesburg, the SABTS started small-scale chromatographic fractionation in 1980 but later stopped production [151].

1.6 CONSOLIDATION IN THE NOT-FOR-PROFIT SECTOR

Difficulties in maintaining viable, sustainable, and local fractionation centers in France and Germany led to significant rationalization in these countries. In France, the regional centers were closed and fractionation was consolidated at Les Ulis (Courtaboeuf, Paris) and in Lille in the form of LFB, the "Laboratoire français de fractionnement et des biotechnologies," in 1994 and became LFB SA in 2005. LFB now toll fractionates for Morocco and Tunisia, as well as for Luxembourg and Brazil. The fractionation center in Strasbourg, once owned by Centeon/Aventis, was acquired by Octapharma in 1999.

In Germany only the unit in Springe/Hannover survived, the fractionation activities of the DRK being consolidated into the Plasmaverarbeitungs GmbH. Octapharma, who had a long-term cooperation with the German Red Cross (DRK) leased the facility in 2008 and later acquired the fractionation plant.

The Central Laboratory of the Netherlands Red Cross (CLB) built new fractionation facilities in Amsterdam in 1975 and a new plant was installed in 1992. Cooperation with the Belgian Red Cross CAF-DCF cvba-scrl (Centrale Afdeling voor Fractionering-Département Central de Fractionnement) was initiated in 1998, the same year that the Sanquin foundation was created, forming a single organization of the blood banks and the Plasma Products Division in the Netherlands under the Blood Provision Act. The Sanquin–CAF-DCF organization is jointly responsible for the fractionation of Dutch plasma (300,000 L) and Belgian plasma (200,000 L) and has an integrated management team. Sanquin has a two-thirds majority in CAF-DCF [114].

In Finland, the Red Cross fractionation plant toll fractionated Estonian plasma until the plant was closed in 2004. Finnish plasma was then fractionated by Sanquin until 2009, when like Norway, Finland contracted the fractionation to Octapharma [152].

In Denmark, the State Serum Institute, founded in 1902, had produced albumin from 1952 and small pool (four donors) coagulation factor concentrates from 1965 [153]. The Institute formed a small capacity fractionation department in 1972 but stopped fractionation in 2004. The American biotechnology company Hemasure acquired

 TABLE 1.1
 The Development of Processing Capacity of the Major Not-for-Profit Fractionators

	Plasma Processed ($\times 10^3$ L/Year)						
Company	1990	1996	1999	2002	2004	2007	2010
LFB	1173	950	600	575	650	655	656
BPL	451	600	500	500	400	450	450
Sanquin	220	220	250	220	220	220	250
CAF-DCF	200	243	198	473	205	400	699
Japanese Red Cross	170	450	480	490	525	550	555
Kaketsuken	185	242	233	249	334	280	250
Korean Red Cross		269	311	340	296	300	230
Total processed	2399	2974	2572	2847	2630	2855	3090

Figures are shown as aggregates following consolidations. Commonwealth Serum Laboratories and ZLB are included in the consolidation of CSL Ltd. Similarly, DRK numbers are shown in the Octapharma table.

Novo's plasma products business in 1996 but the venture was a failure. Denmark now has toll manufacturing arrangements with CSL in Bern.

In 1990, there were 69 not-for-profit plasma fractionation facilities processing approximately 5 million L, 29% of the total plasma fractionated. By 2007, the number of fraction facilities had decreased to 31. In particular, the number of plants in Europe dropped from 39 to 12 and in Asia (excluding China) from 17 to 5. Total plasma fractionated by the non-commercial sector was approximately 6 million L or 24% of the total plasma fractionated. By 2010, the volume had dropped to 4.5 million L with recovered plasma representing 44% of the volume.

The capacity development of the major not-for profit fractionators and the volumes of plasma processed are shown in Table 1.1. In 2010, seven fractionators processed two-thirds of the plasma in the not-for-profit sector. In contrast to the commercial sector these fractionators, with the exception of CAF-DCF, have processed similar plasma volumes over the last two decades. The Japanese Red Cross has developed into an increasingly dominant position in Japan. The development of the smaller fractionators, mostly with a "national" character is shown in Table 1.2.

1.7 THE MULTINATIONAL FRACTIONATION INDUSTRY

Issues with the plasma supply and increasing demand for plasma products in Europe, for domestic use and export, led to European acquisition of American fractionators and plasma collection centers in the 1970s, but these were only a prelude to industry reorganization in 2003–2004, and which continued until the end of the decade [154].

	Plasma Processed ($\times 10^3$ L/Year)								
Company	1990	1996	1999	2002	2004	2007	2010		
Kedrion	650	855	1188	1010	1050	1377	1436 ^a		
Biotest		150	230	200	220	435	1250		
Benesis	350	165	n/a	240	350	280	252		
Korean Green	214	350	529	500	310	200	368		
Cross									
Nihon Pharma		180	200	250	300	b	b		
Kamada	300	n/a	300	n/a	300	200	200		
SK Chemicals		_	_	_	_	270	270		
(Korea)									
Purissmus						300	с		
(Argentina)									
Total processed	1514	1700	2447	2200	2530	3062	3776		

Figures are shown as aggregates following acquisitions. n/a: not available.

^{*a*}Kedrion includes 201,000 L fractionated by Human Bioplazma in Hungary.

^bNihon Pharma processed less than 200,000 L from 2007 onward. ^cPurissmus processed less than 200,000 L in 2010.

In 1996, the two European entities, Hoechst AG who owned Behringwerke and Rhône-Poulenc Rorer who owned Armour, created a 50/50 joint venture plasma products company, Centeon. The company name was changed to Aventis Behring in 1999 when the parent companies merged to form Aventis. Aventis Behring was finally acquired by CSL in 2003 and the name changed later to CSL Behring. CSL also has fractionation plants in the United States, Switzerland, Germany, and Australia (CSL Biotherapies) and along its expansion path had acquired plasma collection facilities in the United States. CSL's operation of multiple facilities or "Centres of Excellence" is illustrated in the "Flood Report" [155].

Baxter's manufacturing strategy is similar to CSL. Baxter had acquired the Austrian fractionator, Immuno AG, in 1997 providing major fractionation facilities in both the United States and Europe and with plasmapheresis centers on both continents. Baxter also operates a facility at Lessines in Belgium, dating back to 1954 when it opened its first European office.

Bayer AG, who had acquired Cutter laboratories in 1974 sold the plasma fractionation assets to Ampersand Ventures in 2005. Ampersand had acquired the former NYBC and the Vitex Melville plant in 2001 and renamed the facility Precision Pharma. Talecris Biotherapeutics was formed from the former Bayer business in N. Carolina to include the Precision facility in New York and therefore remained a uniquely American-based company. Talecris also toll fractionates plasma from Canada. In August 2008, CSL announced intentions to acquire Talecris from Ampersand. Following a negative announcement from the US Federal Trade Commission in May 2009 the merger was abandoned.

Grifols embarked on internationalization of operations in 1960 with a 50% holding of Dade Reagents. The plasma collection centers of SeraCare, now Biomat were acquired in 2002. In 2010, the company had 64 centers in 24 states of the United States. Grifols acquired the assets of Alpha Therapeutic Corporation from The Green Cross Corporation of Japan in 2003 thus providing fractionation facilities in Los Angeles and Barcelona. Following the collapse of the bid by CSL for Talecris, Grifols acquired the company in June 2011 [156].

Octapharma had become established in Vienna in 1989 and in Springe, Germany a decade later. The former CRTS Strasbourg facility in Lingolsheim was acquired in 1999 from Centeon/Aventis. In 2002, the company acquired Biovitrum that had a tortuous history of ownership from Kabi, KabiVitrum, KabiPharmacia, Pharmacia, and finally Pharmacia & Upjohn. A year later, Octapharma acquired the Mexican fractionation company Probifasa SA de CV. The company now has a total fractionation capacity in Europe of 3.2 million L and has announced plans to build a plant in Poland.

The Marcucci Group, which had been a distributor for Immuno AG since the 1960s, adopted the name Kedrion in 1996, after selling the Aima Derivati plant to Immuno and the Sclavo facility to Bayer. Kedrion maintained the fractionation plant of Farma Biagini in Bolognana and the Naples facility previously known as ISI, the Istituto Sierovaccinogena Italiano. Kedrion then had a combined fractionation capacity of 1.3 million L. In 2006, Kedrion announced that it had reached a technology transfer agreement to establish a 300,000 L fractionation facility in Kirov, Russia. Kedrion acquired the Hungarian fractionator Human Bioplazma from Teva in December 2007, adding a further 300,000 L capacity and a plasmapheresis center, and as part of the FTC agreement to the purchase of Talecris by Grifols, acquired the Melville facility on Long Island and two collection centers in 2011 [157] thus marking access to the American market.

In the commercial sector, in 1990 there were 33 plasma fractionation facilities processing approximately 12 million L representing 71% of total plasma fractionation. The number of facilities increased to 45 by 1999, mainly through the evolution of previously state owned facilities in China into corporations. Through rationalization of capacity following a number of acquisitions and mergers the total number of commercial plasma fractionation facilities in 2007 was 34 accounting for 76% of the total plasma fractionation activity or approximately 20 million L of processed plasma. In 2010, the commercial fractionators processed over 29 million L of plasma, more than 80% of which was source plasma.

	Plasma Processed ($\times 10^3$ L/Year)								
Company	1990	1996	1999	2002	2004	2007	2010		
Armour	1175	_	_	_	_	_	_		
Pharmaceutical									
Behringwerke	500	—	_	_	_	_	_		
Centeon	_	3075	_	_	_	_	_		
Aventis Behring	_	—	2480	2700	_	_	_		
ZLB	350	1000	2000	_	_	_	_		
CSL Ltd.	184	305	405	2450	5050	4625	6200		
Total processed	2209	4380	4885	5150	5050	4625	6200		

 TABLE 1.3
 The Growth of CSL Ltd. Through Acquisitions

CSL Ltd. acquired ZLB in 2000. Armour and Behringwerke were merged to form Centeon in 1999. Centeon became Aventis Behring and was acquired by CSL in 2004. CSL Ltd. figures include CSL Bioplasma.

TABLE 1.4 The Growth of Baxter Bioscience

	Plasma Processed ($\times 10^3$ L/Year)							
Company	1990	1996	1999	2002	2004	2007	2010	
Hyland	2600	_	_	_	_	_	_	
Therapeutics								
Immuno	1225	1325	_	_		—		
Baxter Hyland		1950	3550	_		—		
Baxter Bioscience		_	_	3450	3400	4400	5800	
Total processed	3825	3275	3550	3450	3400	4400	5800	

Baxter acquired Immuno AG in 1997.

TABLE 1.5 The Growth of Grifols

	Plasma Processed ($\times 10^3$ L/Year)							
Company	1990	1996	1999	2002	2004	2007	2010	
Alpha Therapeutics	2600	1950	1550	1600				
Instituto Grifols	241	600	880					
Grifols				1080	1768	2000	3200	
Total processed	2841	2550	2350	2680	1768	2000	3200	

Grifols acquired Alpha Therapeutics in 2003 and Talecris Biotherapeutics (shown separately in Table 1.6 in 2011.

 TABLE 1.6
 The Growth of Talecris Biotherapeutics

	Plasma Processed ($\times 10^3$ Liters/Year)						
Company	1990	1996	1999	2002	2004	2007	2010
Melville Biologics	355						
V.I. Technologies		400	565				
Precision Pharma				800	800		
Cutter Biologicals	1625						
Bayer		2100	2350	2350	1910		
Talecris						2110	3600
Biotherapeutics							
Total processed	1980	2500	2915	3150	2710	2110	3600

Melville Biologics, later V.I. Technologies (Vitex) and then Precision Pharma were independent until 2001.

TABLE 1.7The Growth of Octapharma

	Plasma Processed ($\times 10^3$ L/Year)						
Company	1990	1996	1999	2002	2004	2007	2010
DRK	655			_	_		
Blutspendendienst							
DRK	_	600	500	400	_	_	_
Plasmaverarbeitung							
Kabi Pharmacia	160	225	_	_	_	_	_
Octapharma	_	400	1000	1450	1600	2100	3200
Total processed	815	1225	1500	1850	1600	2100	3200

Octapharma acquired the DRK facility in Springe and the Aventis plant in Strasbourg in 1999. The former Kabi facility was acquired in 2002.

Tables 1.3–1.7 show the remarkable developments of the five leading, commercial fractionators: CSL Ltd., Baxter Bioscience, Talecris Biotherapeutics, Grifols, and Octapharma. By 2007 these fractionators processed over 14 million L of plasma, accounting for 70% of the commercial sector and 55% of the 26 million L of plasma fractionated with plant utilization ratios between 52% and 94%. In 2010, the plasma volume fractionated by the top five companies had increased to 22 million L or 75% of the total commercial sector.

1.8 PLASMA FRACTIONATION IN AUSTRALIA: SELF-SUFFICIENCY AND SUSTAINABILITY

The fractionation of plasma in Australia began in the early 1950s when the Australian government determined that there was a need to have plasma products available and manufactured from nationally supplied blood. Arrangements were made for the blood collected from voluntary, nonpaid donors by the Australian Red Cross to be fractionated at the Commonwealth Serum Laboratories in Parkville, Melbourne, with funding for both the collection and fractionation of the plasma provided by the Federal government. The resulting products were to be distributed free of charge to Australian citizens.

The CSL was the logical facility to house a plasma fractionation plant. It had been established in 1916 to ensure that Australia had sufficient supplies of therapeutic sera, including tetanus and diphtheria antitoxin, as well as vaccines and organ extracts, and therefore had the existing infrastructure to establish plasma fractionation on a large scale. The Cohn process was selected and F.J. Dempster, a CSL staff scientist, sent to Cohn's Laboratory at Harvard for 6 months to learn the process. On his return, a manufacturing facility capable of processing 15,000 L per annum was constructed and the first batches of immune serum globulin were issued in December 1953. Batches of normal serum

albumin were issued in July 1954, followed by fibrinogen in 1956, a Factor VIII product in 1961 and a Factor IX complex in 1968–1969.

Over the next 20 years numerous enhancements to the manufacturing processes were made. New products were introduced including an Antithrombin III, a range of hyperimmune immunoglobulin products and an Rh(D) immunoglobulin for the prevention of Hemolytic Disease of the Newborn. By 1989, the processing capacity of the plant had grown to 200,000 L [158] and further expansion on the existing site was difficult. Planning was therefore begun for a new fractionation plant to be built on the outskirts of Melbourne, at Broadmeadows. The new plant adopted a hybrid Cohn-Chromatography process [159,160] based on earlier work conducted by Curling et al. [141,161] at Pharmacia in Sweden in the late 1970s and Friesen et al. [162] in Canada in the early 1980s and came on line with albumin production in 1994. Similar chromatographic processes had already been introduced into South Africa, India, and several European states but the Broadmeadows plant was the largest chromatography-based plant in the world with a design throughput capacity of 250,000 L. Subsequently, a chromatographic process for the manufacture of intravenous immunoglobulin (Intragam P) was developed. Following successful clinical trials and registration, commercial manufacture commenced in 2000. Many of the existing products were improved by the introduction of double viral inactivation steps into the manufacturing processes. The processing capacity of the Broadmeadows plant has continued to be expanded over the ensuing years and in 2010 the plant fractionated approximately 600,000 L of both domestic and international plasma. Planning is now underway to further expand the capacity of the plant so that plasma obtained from other sources can be processed at Broadmeadows to meet the increasing demand for commercial plasma products worldwide.

The Commonwealth Serum Laboratories was privatized in 1994 and its name changed to CSL Ltd. Under the new arrangements, the company retained responsibility for the fractionation of plasma supplied by the Australian Red Cross and entered into an agreement with the Federal government for the provision of this service. Distribution of the fractionated products continued to be undertaken by the Australian Red Cross. In more recent years, the arrangements for the collection of blood and the fractionation and distribution of plasma products in Australia have been the subject of several Federal government reviews. These reviews resulted in 2003 in the establishment of the National Blood Authority (NBA), an Australian Government Agency responsible for ensuring the adequate, safe, secure, and affordable supply of blood and blood products in Australia [163]. More recently the Flood Review [155], released in December 2006, confirmed the roles of both the Australian Red Cross and CSL in the collection, supply, and distribution of blood and plasma products in Australia. These reviews did, however, permit the introduction into Australia of additional plasma-derived products, specifically including intravenous immunoglobulin, when the nationally produced products were insufficient to meet demand. Recombinant DNA products such as Factor VII, Factor VIII, and Factor IX were also included in the funding arrangements of the NBA.

CSL also conducts toll fractionation for a number of other countries in the region. These countries include New Zealand, Hong Kong, Malaysia, Singapore, and Taiwan, although in earlier times plasma from Papua New Guinea and Indonesia was also fractionated.

Following the privatization CSL undertook a series of international acquisitions, purchasing the Swiss Red Cross fractionation facility in Bern, Switzerland in July 2000 and subsequently the plasma products business of Aventis-Behring in December 2003. CSL is now one of the three (CSL, Baxter, and Grifols) dominating plasma product companies in the world with a fractionation capacity of over 6 million L.

1.9 PLASMA FRACTIONATION IN JAPAN: MAINTAINING INDEPENDENCE

Blood transfusion was first performed in Japan in 1919. The Japanese Red Cross (JRC) was established in 1949 and opened its first blood bank in Tokyo 2 years later. During this period, commercial blood banks and public blood centers were also established and flourished at the expense of voluntary donation leading to a campaign to abolish paid donations. By 1963 there were 55 blood banks in Japan, 16 of which were Red Cross and 33 were commercial, corporate, or belonged to foundations [164]. The "Reischauer Affair" [165], in 1964, in which the American Ambassador to Japan became infected with hepatitis as a result of a transfusion following an assassination attempt changed the course of blood collection in Japan. Humiliated by the event, the Japanese Cabinet and then the Diet designated the JRC as the official, not-for-profit collection organization. At the same time the Blood Plasma Corp. of Japan, established in 1950, stopped commercial collection and became the Green Cross Corporation. By 1969, blood was no longer collected from commercial sources. Twenty years later paid collection of plasma ceased and the JRC became responsible for all collection, including the provision of plasma for fractionation, to both commercial and not-for-profit companies.

The JRC fractionation center was established in Chitose, Hokkaido in 1983, a second plant completed at the same site in 1989 and a third unit became operational in 2005 [166]. JRC operates close to its annual capacity of 800,000 L.

The Green Cross merged with Yoshitomi (earlier Takeda) in 1998 and became the Welfide Corporation in 2000.

In 2001, Welfide merged with Tokyo Tanabe, a subsidiary of the Mitsubishi Corporation to become Benesis. Benesis has a fractionation capacity of 350,000 L [167].

Early in 2011, the Japanese Committee on Blood Products, the Pharmaceutical Affairs and Food Sanitation Council, and the Ministry of Health, Labor, and Welfare approved a report regarding the supply of plasma derivative preparations and low level of self-sufficiency (58.7% in 2010). Later in 2011, Mitsubishi Tanabe and the Japanese Red Cross announced plans to integrate their plasma fractionation operations into one not-for-profit enterprise that would also construct a new large-scale facility with the goal of meeting the needs of the entire nation for all plasma products [168].

Kaketsuken, otherwise known as The Chemo-Sera Therapeutic Research Institute, was established in Kumamoto City in the south of Japan in 1945 and opened a blood collection center in 1953. The center was closed in 1967, soon after Kaketsuken commenced fractionation. Nihon Pharmaceutical Co., Ltd. is also a small fractionator in Japan.

For Japan, the import of plasma derivatives (or plasma for fractionation) "presents problems from the standpoint of ethics, safety, and stability of supply" [169]. The JRC collected 1 million L of plasma for fractionation in 2009 but the country reached only a 60% self-sufficiency rate in albumin but 95% for IVIG [170]. To strengthen independence from imports, the Japanese government enacted a law in 2003, named "The Law on Securing a Stable Supply of Safe Blood Products and the Revised Pharmaceutical Affairs Law (Blood Law)" in 2002 [171]. It mandates the national government to instruct the prefectures on the volume of plasma needed for fractionation.

1.10 PLASMA FRACTIONATION IN CHINA AND SOUTH-EAST ASIA

The region containing China and South East Asia is one of the fastest growing economic zones in the world with many countries experiencing double digit growth in recent years. This growth has been fuelled by a collective population in excess of 1.7 billion people, presenting highly competitive labor costs and attracting investment in a wide range of manufacturing activities from steel through to pharmaceuticals. This rapid economic growth has created a burgeoning affluence in sections of this population and enhanced demands for improved housing, education, and healthcare. Within this context it is therefore interesting to note that the only country in the region to have constructed and to operate plasma fractionation facilities is China. The other countries rely on either imported commercial products or in the cases of Hong Kong, Malaysia, Singapore, and Taiwan, collect their own plasma and have it fractionated by CSL Ltd. in Australia.

China has a population of approximately 1.3 billion people, but approximately 70% of the population live in

rural areas and access only about 20% of the total healthcare budget. Until 1985 this large population relied on limited quantities of either imported plasma products or on products produced by a network of State controlled Cohn fractionation facilities, operated by either the China National Blood Products Corporation, the local provincial governments, or the Peoples Liberation Army. The majority of these plants were generally of low operational capacity (less than 100,000 L per annum) and of poor design, well below the GMP standards required of western plasma fractionation facilities.

In 1985, the Chinese health authorities banned the importation of all plasma products except albumin which triggered a period of significant foreign investment into joint ventures operating plasma fractionation facilities in China. In 1996, the military plasma fractionation plants were either transferred to semipublic organizations or were closed down, so that by 1997, the total number of fractionation facilities in the country stood at around 60. Many of these remained, however, with small operating capacities, producing only albumin, and were therefore uneconomic to operate. Further pressure was applied to these fractionators in 1998 when the government issued a directive that all facilities would be required to comply with a new Chinese code of GMP within 5 years or cease operation. As a consequence of this action the numbers of fractionation facilities declined significantly in the following years so that by 2003 there were only 36 fractionators still in operation. More importantly, of these only 16 were operating on a regular basis and only six were producing a diversified product portfolio [172]. By 2008, only 13 of these fractionators remained fully operational [173]. But, as shown in Table 1.8, there are a number of new entrants in the field. The total number of fractionators is now reported to be 25 [174].

Plasma collection in China is controlled by a network of about 200 state or local government-owned centers that collect a total of around 4 million L of plasma each year. The Ministry of Health allocates to each fractionator the exclusive rights to the output of collection centers from three or four separate provinces and in return the fractionators assume the responsibility for the management of the centers and their compliance to government regulations. All of the major fractionators collect plasma by plasmapheresis. Donors are not remunerated and the export of whole plasma is illegal, although partially processed fractions can be shipped overseas for further processing.

In Korea, the government established a policy based on recommendations of "self-sufficiency and exclusion of commercialism" in 1978. The Korean Red Cross (KRC) had plans to establish a new fractionation plant in 1991 but the plan was abandoned. Nonetheless the KRC is a significant fractionator in Korea together with The Green Cross Corporation. Domestic plasma collection accounts for 70%

	Plant	Plasma	Plasma	
Fractionator	2008/2010	2008	2010	Products Produced
Banghe Pharmaceutical Co.	/400		140	Albumin, IVIG, IMIG
Bo'Ya Bio Pharmaceutical Co.	500/1000	300	500	Albumin, IVIG, IMIG
Green Cross China Biologic Products Co.	300	200	100	Albumin, IVIG, Hep B and Tetanus globulins, Fibrinogen, AHF
Guangdong Shuanglin Bio-Pharmacy Co.	/500		100	Albumin, IVIG, IMIG
Henan Zhongtai Pharmaceutical Co.	/500		100	Albumin, IVIG, IMIG
Hua'Lan Biological Engineering Co.	1300	700	290	Albumin, IVIG, Hep B and Tetanus globulins, Factor VIII, PCC, Fibrin Sealant
Hunan Unisplendour Guhan Nanyue Pharmaceutical Co.	—/600	—	100	Albumin, IMIG
Kang' Bao Bio Products Co.	150	100	100	Albumin, IVIG, IMIG
Lanzhou Institute of Biological Products	300/450	200	150	Albumin, IVIG, IMIG
Rongsheng Pharmaceuticals Co. (Chengdu IBP)	800/1000	400	200	Albumin, IVIG, IMIG
Shandong Taibang Biological Product Co.	/500		140	Albumin, IVIG, IMIG
Shanghai Xin'xing Medicine Ltd.	500	200	30	Albumin, IVIG, PCC, Fibrinogen
Shanghai Institute of Biological Products	600	450	230	Albumin, IVIG, IMIG, PCC, Histaglobulin
Shanghai RAAS Blood Products Co., Ltd.	400	250	200	Albumin, IVIG, PCC, Fibrinogen, Factor VIII,
				Fibrin Sealant, Thrombin
Sichuan Yuanda Shu-yang Pharmaceutical Co.	—/600	—	250	Albumin, IVIG, IMIG
Wuhan Institute of Biological Products	200/400	100	140	Albumin, IMIG
Xinjiang Deyuan Bio-Engineering Co.	—/500		100	Albumin

TABLE 1.8The 17 Major Fractionators Out of a Total of 25 Operating in China in 2008 and 2010 Together with TheirOperational Capacity and Throughput in $\times 10^3$ L, and the Products that they Produce

There are seven new fractionators with capacities of 500,000 L or more but throughput volumes are low. Only six fractionators processed more than 200,000 L although capacities are claimed to be significantly higher.

of the supply for fractionation. Products are distributed by the KRC [175].

1.11 INDIA AND THE OBSTACLES TO PLASMA FRACTIONATION

Until the late 1980s, India had nine commercial fractionators. The most modern was the Serum Institute of India, which was constructed in 1985 to produce albumin from human placentae. These small, generally non-GMP enterprises operated in a largely unregulated environment and were reliant on commercial blood donations for their raw material. Recovered plasma was therefore poorly, if at all, controlled with respect to mitigation of risk of viral transmission when the HIV epidemic emerged in India in 1986–1987 among commercial sex workers in Tamil Nadu [176–178].

Officially, India had over 1000 blood banks transfusing 2 million units per year with paid blood donors, donating at least once per month and accounting for half of the demand for blood products [179]. HIV seroprevalence among commercial blood donors was reported to be between 0.2% and

10.3% in 1988–1989 and screening of transfusion recipients and hemophiliacs revealed seropositivity rates between 1% and 12% [180]. HIV screening became mandatory in India in 1988. The Indian government, acting on the recommendations of an expert committee set up in 1989, suspended manufacturing licenses for 16 products made from blood and human placenta pending process modifications to implement viral inactivation. It was also found that all nine companies were noncompliant with HIV screening legislation [181]. This government action essentially ended commercial plasma product manufacturing in India. However, in 1991 up to 17% of blood products including immunoglobulin preparations, cryoprecipitate and albumin from Mumbai and Pune were still found to be HIV positive [182]. In 1996, the government admitted that 25% of blood banks were still unlicensed and the Indian Supreme Court banned "professional blood sellers" [183].

The National Plasma Fractionation Center was established in 1988–1989 to "fulfil a long-felt need for safe plasma products in India." Located in the premises of the King Edward Memorial (KEM) Hospital in Mumbai, the center was established with support from the Swedish International Development Agency (SIDA). Envisaged as a pilot program, the fractionation plant used chromatographic technology to produce immunoglobulin and albumin [184] and had a target capacity of 10,000 L plasma per year [185]. The venture struggled with manufacturing in a non-pharmaceutical environment and finally closed when it was unable to sustain GMP manufacturing standards. There are plans to recommence the project.

Formed from previous blood safety committees, the National AIDS Control Organization (NACO) under the Ministry of Health and Family Welfare took over surveillance and implemented control and safety programs in 1992. "An action plan for blood safety" led to the modernization of 815 blood banks and is the foundation for the safety of the blood supply and therefore plasma for fractionation [186]. The Central Drugs Standard Control Organization (CDSCO) took further control in 1996 with new rules for renewal and licensing of parenteral products, sera and vaccines. CDSCO currently lists 2609 approved blood banks as of June 2009 [187]. The Indian government, through NACO, supported by the German aid organization, GTZ has announced a project to establish a new, 150,000 L plasma fractionation center [188] at a cost of US\$ 56 million to be located in Chennai [189].

Celestial Biologics, a subsidiary of Intas Biopharmaceuticals and with close links to the Prathama Blood Bank in Ahmedabad has plans to establish a fractionation facility [190,191] but currently has contract fractionation arrangements with the Korean Green Cross. In 2010, Reliance Life Sciences ran a small-scale pilot facility in central Mumbai, but had announced plans to expand into a new facility in Navi Mumbai in 2006 [192]. The company now operates a 150,000 L facility running at 50–60% capacity.

1.12 FRACTIONATION IN THE MIDDLE EAST AND NORTH AFRICA

The only country currently operating plasma fractionation facilities in the Middle East and North Africa is Israel where two companies, Kamada Ltd. and Ethicon (previously known as Omrix Biopharmaceuticals Ltd.), which is a division of Johnson and Johnson, operate. Kamada produces Rh(D) and rabies immunoglobulin products from hyperimmune plasma and transferrin and alpha-1proteinase inhibitor from Fraction IV paste using chromatographic technology while Ethicon produces a fibrin sealant, intravenous immunoglobulin, hepatitis B immunoglobulin, and albumin in a cold ethanol plant that has a throughput capacity of around 100 tons per annum [193]. Plasma is collected by the Magen David Adom (Israeli Red Cross) from voluntary donations and the remuneration of plasma donors is illegal. Plasma products are also purchased from the major commercial fractionators on a tender basis [194].

In Egypt, the Egyptian Organization for Biological and Vaccine Production (Vacsera) operated a pilot plant at Agouza on the outskirts of Cairo from 1976 to 2001. The capacity of this plant was, however, limited to 5-8000 L plasma per annum and used a Cohn process to produce 15% albumin, 4% purified plasma fraction, and 16% intramuscular immunoglobulin. The plant was closed down in 2001 when the Egyptian government initiated a program to build a new fractionation plant on the Vacsera site. The initial capacity of the plant was to be 60,000 L annually but incorporated plans to expand throughput to 150,000 L at a later stage. The fractionation technology was to be supplied by the SNBTS and the project managed by the French contractor Lebas. The venture encountered significant operational difficulties however, Lebas exited the project and the SNBTS contract was not extended after 2003. In 2005, Vacsera was partially privatized but the project has yet to be restarted [195].

Egypt collects approximately 250,000 L of blood annually. Of this, 80% is collected by the Ministry of Health while the remaining 20% is collected by the armed forces and the University Hospital. In the late 1990s, a major initiative was undertaken by the government to improve the quality of the blood collection service. The Swiss Red Cross was contracted to review the Egyptian blood service and institute changes to bring the collection of blood up to international standards. The Swiss government financially supported this initiative. Payment of blood donors was banned and all commercial blood banks shut down. This initiative resulted in the creation of the National Blood Center in 2000. The NBC has around 240 blood banks that collect 60-70,000 L/year, all of which is separated into components. In addition, the government hospitals collect around 120,000 L per annum. Vacsera uses plasmapheresis to collect between 2 and 6000 L of plasma per annum. The Egyptian government has been seeking an international fractionator to convert this plasma into a full range of plasma products [172].

In Saudi Arabia (KSA) there have been a number of proposals over the last 20 years aimed at establishing a fractionation facility capable of processing plasma collected from the Kingdom and the Gulf States. The concept was originally proposed by a private company called the Saudi Pharmaceutical and Appliances Corporation (SPIMACO) in the early 1990s. This model envisaged a system similar to the Australian model where the plasma was collected by the State, toll fractionated by SPIMACO and then returned to the State for distribution. There was, however, concern over the privatization of the plasma fractions business and the project did not progress.

An alternative proposal was put forward by the King Saud University that envisaged a 150,000 L plant producing albumin, IVIG, Factor VIII, and Factor IX. Under this arrangement the products would be sold back to the hospitals at prices determined by the Ministry of Health. Eighty-five percent of the funding was to be obtained from the private sector while 15% was to come from the MoH. SPIMACO entered into discussions on this proposal and in 2002 formed the Saudi Arabian Plasma Group (SAPG) with King Saud University and Sultan Bin Abdulaziz Al-Saud Foundation. The Sultan Bin Abdulaziz Al-Saud Foundation supports hemophiliacs in the KSA.

In 2004, a contract was awarded to Further Options Pty. Ltd. to prepare a Feasibility Study for the SAPG that had as criteria that the plant would have a capacity of 250,000 L, that Factor VIII, Factor IX, albumin, and IVIG would be produced, that the plasma would be sourced locally, and that the technology would be chromatographic, not Cohn. The Feasibility Study was completed and the financial analysis established that the plant was a financially viable proposition. The project was, however, delayed by a series of events including the death of King Fahd and the restructuring of the SAPG in 2007 but has yet to progress further. In addition, there have also been reports of proposals for the construction of a plasma fractionation plants in the UAE and in Jeddah, but these have also yet to move forward [172].

The Iranian Blood Transfusion Organization collects over 1.8 million units of blood from voluntary, nonremunerated donors. The associated, non-profit Iranian Blood Research and Fractionation Company suspended fractionation in the 1990s due to its poor viral inactivation techniques. Currently, about 75,000 L of plasma are sent for toll fractionation and there are plans to expand collection and move toward selfsufficiency, potentially with a national fractionation facility [196]. Biotest also has plasma collection centers in Iran.

1.13 THE PLASMA FRACTIONATION INDUSTRY IN 2010–2011

The first industrial scale plant at Armour Pharmaceutical in 1943 had capacity to process plasma from 8000 blood donations/week or approximately 100,000 L per annum [86]. Now, in 2011, the major commercial fractionators have annual capacities of 4–6 million L. With the exception of the Japanese Red Cross and LFB in France, the non-profit and government-supported centers have capacities in the 100,000—600,000 L range.

Three companies dominate the fractionation industry— Baxter Bioscience, CSL Ltd., and Grifols (now including Talecris). Together, these companies are responsible for manufacturing about 70% of the plasma-derived products in the world and they plan to significantly increase capacity through to 2014 [197]. The global fractionation capacity is estimated at over 40 million L with a capacity utilization of ca. 80%. Not-for-profit manufacturers had an estimated throughput in 2010 of 8.4 million L compared to the commercial sector's 23.5 million L or 73% of the total plasma fractionated [198]. There were about 65 fractionation plants in the world in 2008 of which 65% were commercial enterprises.

More than two-thirds of the plasma processed by the industrial fractionators is source plasma whereas the not-for profit sector processes one-third source plasma and twothirds by recovered plasma. Approximately 21 million L or 71% of the plasma fractionated is source plasma and 29% is recovered plasma. Collection of plasma in North America totals 18 million L, 7 million L are collected in Europe, and 4.7 million L are sourced in Asia: the United States therefore contributes about 60% of the global plasma supply [199]. A self-sufficiency plan, based on remunerated plasmapheresis, at the European level rather than an individual level of EU member states is seen as necessary [200]. Thirty years ago there were almost 400 collection centers in the United States with a third owned directly by fractionation companies. The number of US collection centers runs in cycles. Sixty centers were closed in the 5-year period from 1979 to 1984 [201] and there was further rationalization in the period 2002–2006 when there were less than 300 centers in operation but the number increased to 375 in 2008 with a further 68 new openings planned [202]. At the end of 2010 there were 413 US centers in operation with at least three-quarters owned by the major fractionators. The supply dominance of the United States, the multinational nature of the dominant industries and the toll manufacturing solutions to national supply call for an unprecedented revision and harmonization of regulatory control [203]. The variability of plasma for fractionation is dramatic, depending on collection practices [204] and the antibody spectrum as well as the IgG titer, which varies with the exposure of the donor population to pathogens.

Albumin dominated the production of plasma proteins throughout the first decades of the industry and demand is still high with 500 metric tons produced annually after the industry had recovered from the doubtful conclusions of the Cochrane Study [205]. Usage rates vary widely: in 2008, Italy consumed 600 kg/million population, Germany and the United Kingdom 148 and 118 kg/million, respectively. The average consumption in Europe (26 countries including Russia) was close to 200 kg/million and the average rate of increase was 15% between 2005 and 2008 [199]. Chinese consumption is considered to be low at 100 kg/million where albumin accounts for 60% of the plasma product market [206].

The plasma fractionation industry manufactures about 100 metric tons of immunoglobulin and production is forecast to increase particularly if products, currently in clinical trials for Alzheimer's disease, are approved. The use of immunoglobulins was revolutionized by the development of intravenous products in the 1960s and the developing alternative of subcutaneous use and therefore the possibility of home treatment promises well for the future. The average use of IgG in Europe is 36 kg/million population. However, excluding former eastern European countries the average is close to 64 kg/million. The overall rate of increase (2008/2005) varies from 149% in Russia to -4% in the United Kingdom [199]. The need for normal immunoglobulins now determines the volume of plasma needed for fractionation and P. Robert calculates that close to 40 million L of plasma will be collected in 2015 [207].

The plasma fractionation industry was significantly affected by the introduction of recombinant Factor VIII in 1993. In that year the industry supplied about 1.8 billion IU Factor VIII. Although the market share of plasma-derived Factor VIII has been reduced, the demand for plasmaderived coagulation products continues to grow (on average at 8%/year), particularly in developing countries where the importation price of recombinant alternatives is at a premium. The market had grown to 2.4 billion IU by 2007 and the industry output could exceed 3 billion IU in 2015. Total Factor VIII use (plasma derived and recombinant) was 5.2 IU/capita in the United States and the United Kingdom in 2005, 2.8 IU/capita in Japan, and 1.2 IU/capita in Brazil [208]. In China, as in many other countries, the use is <0.1 IU/capita and less than 10% of the estimated 80,000-100,000 hemophiliacs receive treatment [209].

Although immunoglobulin, albumin, and Factor VIII drive the plasma products industry, there are many other products of plasma that are manufactured for rare bleeding disorders and other hereditary and acquired diseases. These include von Willebrand Factor, Factors IX, XI, XIII, fibrinogen, antithrombin III, Protein C, alpha-1-proteinase inhibitor, C-1 esterase inhibitor, and plasmin and established fractionators have a pipeline of new products. In addition, there is a significant need for anti-D (Rh) IgG and an expanding demand for hyperimmune products for both infectious diseases as well as to meet the threat of bioterrorism.

Thirty years ago, a group of plasma fractionation experts representing Cohn's laboratory, the US FDA Bureau of Biologics (now CBER), the American Red Cross, the notfor-profit fractionators, and the commercial sector met in Bern to discuss the future of the industry, particularly developments in manufacturing procedures and the impact of recombinant DNA technology. J.S. Finlayson concluded that "It requires little imagination to foresee a time at which 'plasma derivatives' will no longer be derived from plasma" although no immediate effect was forecast. Biotechnology was seen as potentially immensely powerful but F. Rothstein commented that "the evidence is overwhelming that 'ethanol fractionation' with other appended methods can serve the function of providing safe and efficacious plasma protein derivatives" [210]. In 2011, we see a dynamic future for the plasma fractionation industry, combining recombinant DNA and hybridoma techniques with continuing development of purification and pathogen reduction technologies that will provide further human blood plasma-derived therapeutic proteins.

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