Worldwide Supply and Demand of Plasma And Plasma-Derived Medicines

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1) The Early Years of the Plasma Industry

In the early 1940's, Dr. E. Cohn discovered the plasma fractionation process in Boston (1). After it was found that albumin was an efficacious and safe drug, and could be produced in large quantities, several manufacturing plants were built in the United States. Pharmaceutical companies involved at the early stage of the fractionation industry included Parke Davis, which built a plant in Los Angeles (now operated by Grifols), Armour near Chicago, now operated by CSL Behring, Cutter in Berkeley, and Baxter in Glendale, near Los Angeles. Some public entities also built facilities to process human plasma, such as the Michigan Biological Laboratory. In Europe, fractionation plants were built in Germany (Behringwerke, part of the Hoechst pharmaceutical concern), Italy (Farma Biagini, Sclavo), France (Centre National de Transfusion Sanguine and Institut Merieux), Grifols in Spain, and the Swiss Red Cross Blood Transfusion Service in Switzerland (2). In Japan, the Green Cross corporation built the first fractionation plant in Asia (3). These facilities began producing albumin, and some "normal" (polyvalent) or specific immune globulin preparations, such as anti-tetanus, anti-hepatitis B, anti-rabies immune globulin, and others. Rho(D) immune globulin was discovered in the late 1960's, as were antihemophilic factors VIII and IX.

2) Plasma Supply: Emergence of the "Source" Plasma Collection Sector in the United States

Initially, the Red Cross and other non-profit blood transfusion services supplied plasma, but they were soon unable to supply sufficient quantities for the fractionation plants, which were gradually expanded. As a result, a business sector focusing exclusively on collecting plasma for fractionation began to emerge in the United States, comprising a myriad of private plasma collection organizations. This sector's growth was spurred by the fact that plasma

donors were allowed to donate relatively frequently: twice a week, with a two day interval (4), corresponding to about 65 liters per year, whereas the donation frequency authorized in most other countries was such that the maximum volume of plasma that could be donated by an individual was 15 to 18 liters of plasma per year (5).

Until the mid-1980s, plasma was collected in bags and separated from whole blood by centrifugation. The introduction of automated plasmapheresis machines in the 1980's increased the donation process' safety and efficiency (6). The plasma collected from these centers was called "source", while the plasma obtained from whole blood was called "recovered plasma". Outside the U.S., the supply of plasma remained mainly with the blood transfusion services. In Austria and Germany, legislation allowed more frequent donations.

In the 1980's, the AIDS crisis led to a complete transformation of the plasma collection sector and of the fractionation industry in the United States.

In 1978, 5.4 million liters of "source" (apheresis) plasma were collected in the United States. This volume increased to almost 12 million in 1996, then declined to 9.6 million in 2000, due to, among others, the closing of some fractionation plants as a result of the strict enforcement of "good Manufacturing Practices" (GMPs) by the U.S. regulatory authorities (Food and Drug Administration) (7). The volume of source plasma directly depended on the needs for finished products.

3) From Albumin to IVIG: the "Market Drivers"

Until the 1970's, the fractionation plants produced as much albumin as the market required, and they purchased the quantities of plasma they needed to meet the production requirements for this protein. Albumin was the market driver. When plasma-derived factor VIII began to be commercialized in the late 1970's, it became the market driver because larger volumes of plasma were needed to meet the demand for it. By that time, the U.S. fractionators produced albumin, intramuscular immune globulin and coagulation factors for the domestic market as well as for export because the U.S. fractionation plants were significantly larger than those operating in other countries. At the beginning of the 1980's, intravenous immune globulin (IVIG) was introduced in the United States. It became the market driver in the 1990's when plasma-derived factor VIII, and soon, factor IX, were replaced by recombinant products. The demand for albumin, factor VIII, and since the

early 1990's, IVIG, determine the volume of source plasma collected.
For this reason, the volume of plasma has shown wide variations over the years, while the fact that source plasma donors were compensated also contributed to these variations. In contrast, the quantity of recovered plasma for fractionation obtained from separation from whole blood remained remarkably flat over the years because its volume depended on the needs for labile blood components, in particular red cell concentrates and, increasingly, platelets.
Similar observations can be made in other regions: in Asia and Pacific, source plasma is mainly collected in China, where the quantity of plasma collected is also determined by the need of the domestic plasma industry. In 2005, some 4.5 million liters of plasma were collected in China. As the plasma industry was subjected to a strict enforcement of the good manufacturing practices by the regulatory authorities (SFDA) following the discovery of contaminated products, similar to events that occurred in the U.S. in the late 1990's, the volume of source plasma collected dropped to 2.7 million liters in 2007, and climbed again to about 3.4 million liters in 2009. Recovered plasma cannot be used for fractionation in China. No other country in the region collected plasma for fractionation in any significant quantities (8).
In Europe, the quantity of source plasma for fractionation only increased in recent years, from less than a million liters to about 2.5 million liters in 2009. The commercial fractionators mainly processed source plasma imported from the U.S.

4) Recovered Plasma: An Untapped Source of Life-Saving Medicines

In the blood collection sector, the priority given to the procurement of adequate quantities of labile components, notably red cells and platelets, tends to relegate plasma to a low priority. The term of "recovered" plasma is in itself rather diminishing, as if it was a by-product – which it is many blood centers. Yet, recovered plasma is just as good as source plasma to produce therapeutic proteins, if not better in the case of some of them. From one liter of plasma, whether source or recovered, a fractionation plant can produce, according to generally agreed production yields (9):
- 25 to 28 grams of albumin,
- 150 to 200 international units of factor VIII (possibly more in the case of source plasma which is frozen immediately after collection),
- 250 to 300 international units of factor IX
- 3 to 5 grams of intravenous immune globulin (possibly more in the case of

recovered plasma)
- 250 international units of antithrombin III
- 0.20 grams of alpha-1 antitrypsin, and
- Various quantities of hyperimmune globulin products, assuming that an adequate antibody titer is present in the plasma

In a number of countries, in particular in developing countries, the blood centers' focus on supplying hospitals with labile components has turned plasma into a "forgotten" commodity. The need for red cells and platelets requires the blood centers to collect a certain number of blood units to cover hospitals' needs. The quantity of whole blood collected is such that some plasma, generally fresh frozen, remains unused. Some units of fresh frozen plasma are delivered to hospitals to treat patients with coagulopathies and other conditions, but the leftover plasma units are stored and eventually jettisoned. This plasma could well be sent to a fractionator, whether domestic of foreign, to manufacture life-saving plasma-derived medicines.

In some parts of the world, especially in emerging countries, the collection standards do not match those required by the fractionators. As they are under the obligation to follow strict rules and regulations regarding the quality of their operations, starting with the quality of the raw material, the fractionators must be very selective about the plasma they use. For instance, the European health authorities (10) require that the plasma pool for fractionation be tested for HIV, Hepatitis A, B and C, and Parvovirus B 19. The blood collected by many centers around the world is often unable to comply with these regulations, causing some recovered plasma to be unused. Other problems include logistics, including the storage of the plasma and its shipment to a fractionation facility. These obstacles are not insurmountable, as illustrated by the contract fractionation between private or public fractionators and blood transfusion services in Brazil, Iran, Hong Kong, Singapore, Taiwan, and Tunisia, to name but a few. This requires the blood centers to upgrade their collection standards, which is a worthwhile endeavor considering the clinical and financial value of recovered plasma. Furthermore, this is also owed to the donors, who deserve that their donation be fully used without waste. In Colombia, a country where the collection standards are among the top in the region, approximately two thirds of the recovered plasma is not used. This represents close to 90,000 liters of plasma per year, the value of which may be estimated at roughly $12 mil-

lion. The fractionation of this quantity of plasma would have a market value in excess of $24 million (11).

5) Worldwide Demand for Finished Plasma-Derived Medicines

In 2009, the worldwide demand for plasma-derived medicine was estimated at $11.8 billion, IVIG representing 46% of the total, albumin 10% and factor VIII, 9% (Chart 1) (12).

Plasma-derived medicines are primarily used in the industrialized countries, due to the comparatively high cost of therapy. For example, the European market, which only had 11% of the world population, represented close to 36% of the world market, while the Asian & Pacific market represented 15%, with 58% of the world population (Charts 2 and 3). These discrepancies are illustrated by wide variations in per capita usage (Charts 4 and 5).

In the case of polyvalent intravenous immune globulin (IVIG), such variations are caused by product availability, financial access to therapy or insurance coverage, price, authorization to prescribe for certain non-approved indications, product awareness, and more importantly, diagnosis of the conditions for which IVIG is indicated. As for coagulation factors, it is often a function of government's ability and willingness to cover hemophilia care. Lobbying activities by patients groups play an important role in this regard.

6) Matching the Demand for Finished Plasma-Derived Medicines and the Supply of Plasma

Over the past few decades, the plasma industry has been able to supply the worldwide markets for plasma-derived drugs in most industrialized countries. Financial constraints have caused the low usage level recorded in the other countries, rather than limitations in the availability of plasma (source or recovered) or in fractionation capacity. Recent surveys show that the latter is sufficient to meet the needs in the coming years, as the fractionators can react relatively easily and quickly to a demand surge. As for the plasma, experience has shown that it is possible to increase the collection levels of source plasma in the United States relatively easily, provided that the necessary funding is available.

In 2010, 78 fractionation plants were operating in the world, 25 of which were in China (which in fact has 35 licensed plants – some of which operate only sporadically), 26 in Europe, and 8 in the United States, the latter fractionation plants being of a larger size than those operating in other regions.

The global fractionation capacity was

about 48.4 million liters, and the recorded volume of plasma fractionated (source and recovered), 33.6 million liters, including 29.1 million liters processed by the commercial sector, and 4.5 million liters by nonprofit organizations. In the past decades, the fractionation industry has undergone three major trends: privatization (there are more commercial fractionators than ever), increase in processing volume (higher fractionation capacity) and increased productivity through higher yields.

7) Conclusion: Improving Global Access to Plasma Derived Medicines

Plasma-derived medicines produced today are safe, efficacious and available in large quantities. The cost of therapy remains the main barrier for access to these drugs in the emerging countries. The use of recovered plasma which is currently destroyed by many blood centers could alleviate some of these barriers in some countries.

Figure1

THE WORLDWIDE PLASMA FRACTIONS MARKET BY PRODUCT - 2009

WITHOUT RECOMBINANT FACTORS

Total Market $11,778.8 Million

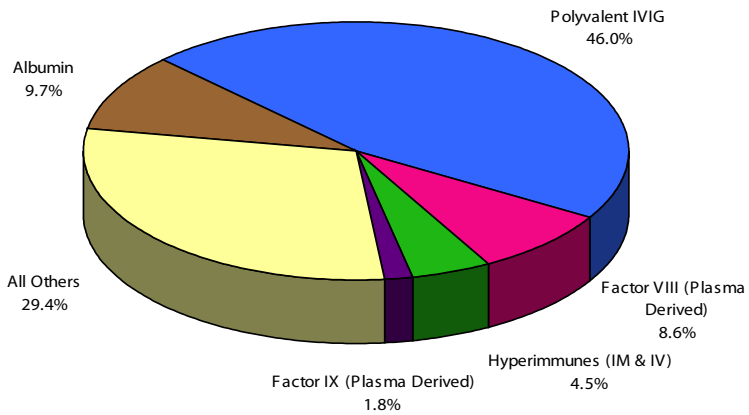

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Figure 2

World Population by Region - 2010

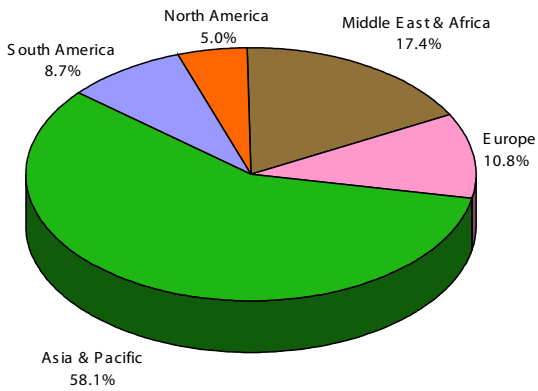

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Figure 3

THE WORLDWIDE PLASMA FRACTIONS MARKET BY REGION - 2009

WITHOUT RECOMBINANT FACTORS

Total Market $11,778.8 Million

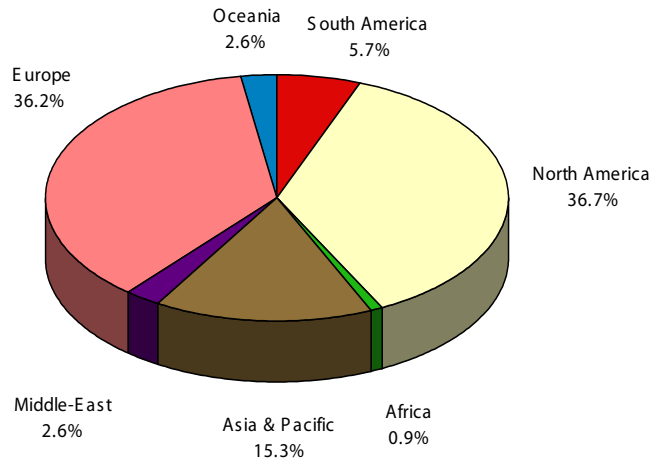

Figure 4

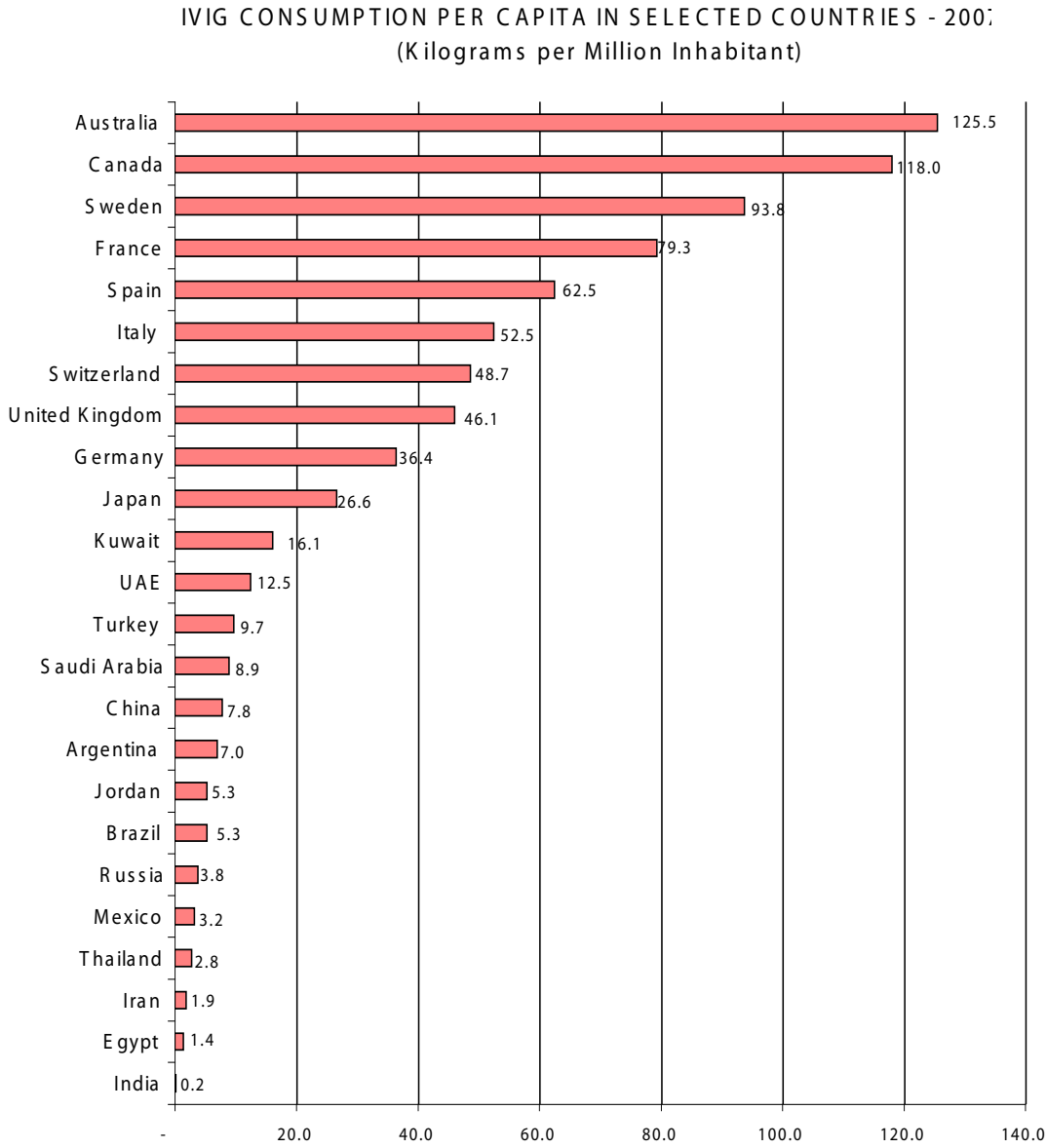

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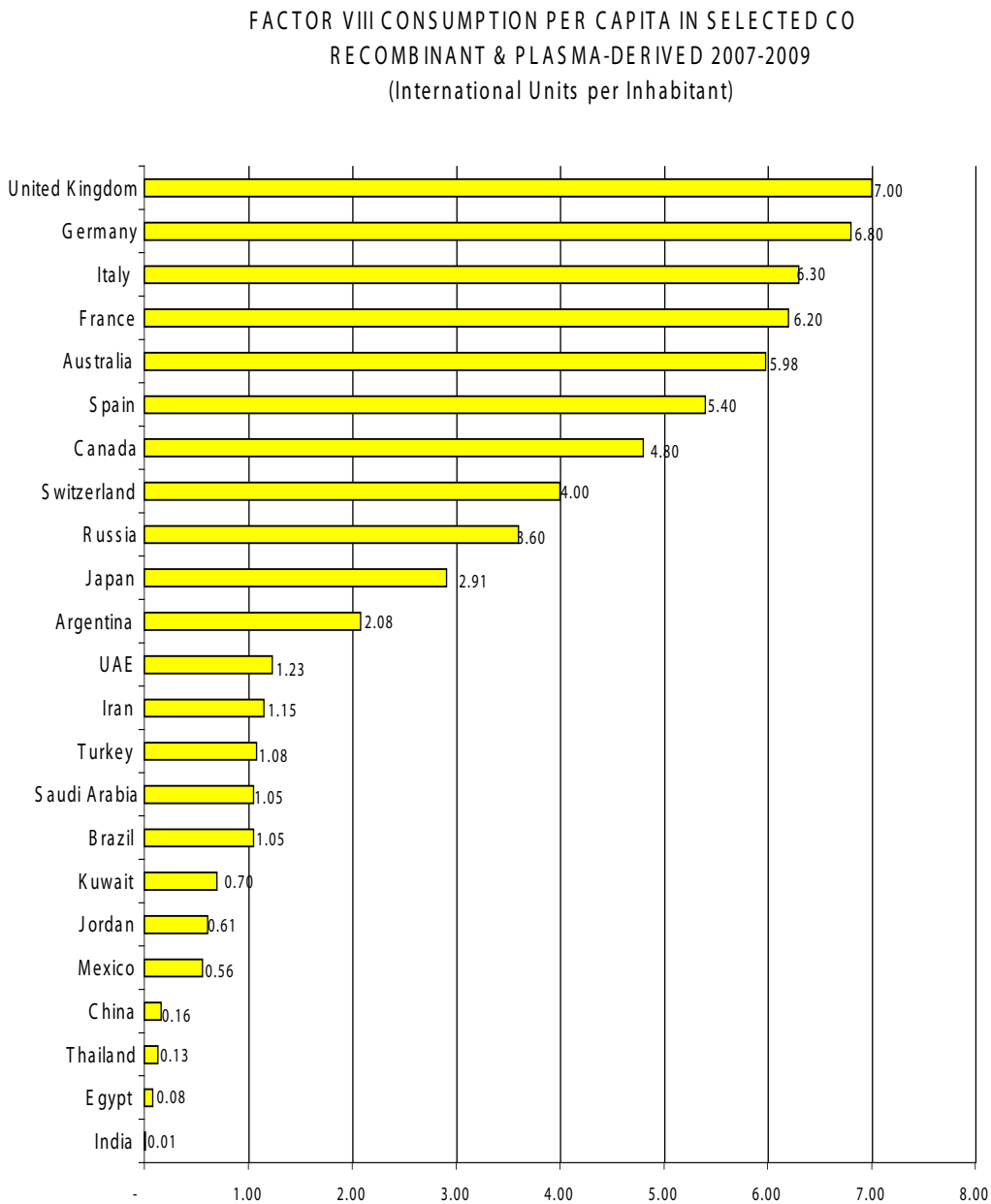
Figure 5



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