Biologicals 38 (2010) 81–86

Contents lists available at ScienceDirect

Biologicals

journal homepage: www.elsevier.com/locate/biologicals

Improving availability and affordability of plasma-derived medicines

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ARTICLE INFO

Article history:
Received 22 October 2009
Accepted 23 October 2009

Keywords:
Plasma fractionation
Plasma-derived medicines
Availability
Affordability

ABSTRACT

Plasma contains several therapeutically important proteins. Currently more than 25 of them are commercially available to treat life-threatening diseases. Some of these medicines already included in the *WHO Model List of Essential Medicines* indicating their importance from a global perspective. However, unfortunately due to very high cost of treatment with plasma-derived medicines, these clinically precious tools are not affordable for a majority of the patients living in developing countries. There are some options available for securing accessibility to these medicines. These include local production, importation and contract fractionation of locally produced plasma. Although local production of plasma-derived medicines and/or importation of these medicines might be a practical approach to respond to the needs for these medicines, in recent years several countries have used contract fractionation of locally produced plasma as a very effective approach for improving availability and affordability of plasma-derived medicines in their national market.

1. Introduction

Plasma, the clear protein-rich fluid which is left behind when platelets, red blood cells, and white blood cells are removed from blood, contains therapeutically precious proteins. Plasma proteins constitute around 7% of the blood volume. Although there are more than 300 different proteins in plasma currently only 25 have been recognized for therapeutic purposes and are commercially available and used for treating the life-threatening diseases or injuries such as bleeding and thrombotic disorders, immunological diseases, infectious conditions as well as tissue degenerating diseases. The most important plasma-derived products are coagulation factors, albumin, immunoglobulins, sealants and protease inhibitors.

The fact that WHO has included plasma-derived medicines (PDM) in the *WHO Model List of Essential Medicines*, reflects the international consensus on the importance of these medicines in treating life-threatening diseases. However, it should not be forgotten that plasma protein therapies are still very expensive and often inaccessible to the patients living in countries with limited resources available to the health sector. Therefore, today economic status of the nations and not needs of the patients, influences the distribution and usage of these therapeutic products. Availability and affordability of these products are very much influenced by national policies on price control and reimbursement schemes. Although there are some biotechnology-derived coagulation factors available in the market, financial constraints have impeded the access to these products in developing countries. Therefore it seems that patients living in these countries should rely only on plasma-derived antihemophilic factors for the time to come.

Coagulating factors including factor VIII (FVIII), factor IX (FIX), von Willebrand's factor, fibrinogen, fibrin sealants (comprising fibrinogen-rich and purified thrombin concentrates), prothrombin complex concentrate (PCC; mixture of vitamin K-dependent coagulation factors including factors IX, II, X, protein C, protein S and sometimes FVII), factor XIII, factor XI concentrate and specific concentrates rich in factor VII with reduced amount of other vitamin K-dependent clotting factors are among the most used PDM around the world. Human thrombin concentrates prepared by activation of the PCC are available in the market and are used as component of fibrin sealant [1].

Coagulation factors are key medicines for management of hemophilia. Hemophilia is a "rare" and chronic disease with global distribution both in developed and developing countries. Management of hemophilia needs special attention from national health services. Antihemophilic medications are expensive and depending on severity and treatment regimen, may account for 45–93% of total care costs. HIV and HCV coinfection has been associated with increased morbidity, mortality, and clotting factor

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1045-1056/$36.00
doi:10.1016/j.biologicals.2009.10.004

utilization in hemophilia patients [2]. Currently there are two main approaches available for replacement therapy in hemophilia patients. In "on demand" therapy method, coagulation factors are used to stop bleeding based on as-needed. However, "prophylactic" replacement therapy is based on regular administration of coagulating factors to prevent bleeding. Although on demand therapy is less intensive, there is a risk that bleeding will cause damage before therapy is given. It is obvious that the prophylactic method is more expensive than on demand therapy.

Albumin is one of the most commonly used PDM. Albumin has several physiologic functions but with better understanding of the pathophysiology of diseases the use of albumin in clinical practice has become more controversial and despite six decades of clinical investigations the value of albumin administration is increasingly being questioned. However, current applications of albumin include volume replacement therapy, support of colloid oncotic pressure, maintenance of serum albumin levels (in hypoalbuminemia) as a transport molecule, free radical scavenging and maintenance of membrane integrity, management of fluid shifts as an osmotic agent in severely burned patients and liver diseases with ascitis [3].

Immunoglobulins are perhaps the most important PDM. They have been used since 1952 to treat patients with conditions of immune deficiency and chronic lymphocytic leukemia. The first immunoglobulins were administered intramuscularly. In the early 1980s intravenous preparations of immunoglobulin (IVIG) were used to treat patients with idiopathic thrombocytopenic purpura, an autoimmune condition causing platelet deficiencies. Today, IVIG is used in many different autoimmune disorders. IVIG typically contains more than 95 percent unmodified IgG with intact immune signaling functions along with trace amounts of IgA and IgM, cytokines, soluble complement, and HLA molecules. IVIG is approved for treating primary immunodeficiency, autoimmune thrombocytopenia, the vascular disorder, Kawasaki disease, hematopoietic stem cell or bone marrow transplantation in patients older than 20 years, chronic B-cell lymphocytic leukemia, prevention of graft versus host disease in transplant patients, and pediatric HIV-1 infection. IVIG is also used off-label in the treatment of aplastic anemia, red blood cell aplasia, autoimmune hemolytic anemia, hemolytic disease of the newborn, patients with acquired clotting factor inhibitors, acquired von Willebrand disease, immune-mediated neutropenia (deficiency of polysegmented white blood cells), pemphigoid disorders, refractoriness to platelet transfusions, blood transfusion reactions or consequences, Graves' ophthalmopathy, pretibial myxedema, multiple sclerosis, CIDP, and various systemic autoimmune rheumatological conditions including rheumatoid arthritis, dermatomyositis and systemic lupus erythematosus (SLE), and in patients at risk for infectious diseases because of compromised immune systems such as patients with burns, trauma, low birth weight or HIV infection [4]. Currently IVIG use for labeled and unlabeled indications is growing steadily and its global consumption could reach several hundred tons annually.

Alpha-1-antitrypsin, protein C (PC) and C1-esterase inhibitor are among the clinically useful PDM. Alpha-1-antitrypsin deficiency is a relatively common but under-recognized genetic disease which may predispose individuals to several serious illnesses, most commonly emphysema beginning in the third or fourth decade of life that less frequently may result in liver disease or a skin disease called panniculitis. It is estimated that as many as 95% of people with Alpha-1-antitrypsin deficiency have not been identified. The heterozygous carrier state for the mutant Z gene was found in 1.5% to 3% of the population [5]. Alpha-1-antitrypsin is indicated in the treatment of patients with lung disease secondary to genetic deficiency of Alpha-1-antitrypsin as replacement therapy. There are now several commercially available Alpha-1-antitrypsin concentrates in the market.

PC is a vitamin K-dependent proenzyme with anticoagulant activity, and patients with congenital PC deficiency are at high risk for thrombotic episodes. There are some PC concentrates commercially available for management of rare cases of congenital homozygous PC deficiency who present with severe clinical condition in early infancy. C1-esterase inhibitor concentrate is generally purified by chromatography from the cryopoor plasma after extraction of PCC and are used in acute phases of angioedema in patients with congenital or acquired C1-esterase inhibitor deficiency.

2. Global market

The global market for PDM is a dynamic market growing about 10% each year. However, it should be noted that North America and Europe with less than 20% of world's population consume more than 75% of the total PDM [6].

Introduction of recombinant coagulation factors in recent decades has created a substantial shift toward use of these products in wealthy nations. However, financial constraints have impeded access to these products in developing countries. Recognizing that 80% of people with bleeding disorders are living in developing countries, it becomes clear that the delivery of the PD antihemophilic factors will be the main therapeutic option available in the developing world for the foreseeable future. It is obvious that successful treatment of patients in need of PDM requires strong support of governments, insurance companies and patient advocacy groups.

Although per capita usage of FVIII worldwide is increasing, the trend is more pronounced in emerging economies. This might indicate improving care for hemophilia patients living in these countries. Between 2002 and 2007 there was a 35% increase in the number of identified patients and a 63% increase in factor use from 0.80 IU per capita in 2002 to 1.32 IU per capita in 2007. Despite this, it is reported that about 70% of patients with bleeding disorders have not been diagnosed worldwide and only 25% of diagnosed patients receive proper treatment [7].

The past two decades have seen dramatic changes within the global plasma industry. Mergers and acquisitions, the development of recombinant alternatives for existing plasma products, and increasing levels of regulation with respect to product safety are among the most important developments of the field. It seems that the United States is the only country that is totally self-sufficient in plasma and PDM. Some 70% of the plasma fractionated globally is collected in the United States. In other countries, arrangements for the collection of plasma, and for its subsequent fractionation, reflect domestic demand together with various economic, demographic and historical factors.

Although, it is reported that 23–28 million liters of plasma are fractionated each year in the world and about 35% of these amounts of plasma are "recovered" plasma (from donated blood), it is estimated that at least 5.8 million liters of recovered plasma are destroyed, mainly in developing countries [8]. Global production of plasma for fractionation in 2007 increased by 20% compared to 2005 (Table 1) [9]. However, compared to recovered plasma, the role of source (apheresis) plasma in this increase is more pronounced. Currently the annual global plasma fractionation capacity is approximately 34 million liters. Although about 20% of this capacity belongs to the state-owned and not-for-profit fractionators, commercial enterprises mainly located in Europe and United States are the major players of the PDM market [6]. In recent years, mainly due to mergers among fractionators, the number of

Table 1
Plasma collected for fractionation worldwide (l × 1000).

Year	Recovered	Apheresis	Total
2005	7890	14,228	22,118
2007 (% increase)	8634 (10%)	17,984 (26%)	26,582 (20%)

fractionators has decreased while the capacity to process plasma has increased [7].

In contrary to the conventional pharmaceuticals, production cost of PDM is much higher and estimated to be about 65% of the product price. This is mainly due to the high cost of the raw material. Price of plasma as the main starting material for production of PDM is a major contributor to the final price of PDM. Therefore any attempt to improve quality and safety of the plasma produced in developing countries to be used for fractionation would be considered a substantial step toward improving availability of the PDM in these countries. Production of sufficient quantity of qualified plasma for fractionation is the key element in availability of PDM. Therefore, the main goal should be to use all recovered plasma available in the country, which is very cost effective and can contribute to improve the overall quality of health care services.

Production of recombinant coagulation factors has played a critical role in changing PDM market shape. This change could end up in two different scenarios. Some experts believe the increase usage of recombinant factors by patients in developed economies may create the opportunity for patients living in emerging economies to have access to PD coagulation factors at lower cost. This is because commercial fractionators could account on IVIG as the plasma collection driver for developed economies and produce PD coagulation factors as by products at lower marginal cost [10].

Other experts believe that the new market driver in rich countries is recombinant factors that will diminish economic interest of commercial fractionators to manufacture PD coagulation factors which remain mainstream therapy for patients in developing countries. Therefore these patients might face a decreased supply of factor concentrates and ultimately an increase in price of these products. It is believed that the assumption that decreased use of PD FVIII or FIX in developed countries would increase the supply of products to developing countries may not be economically viable [1]. In fact in this scenario as fractionators will determine price of plasma based on fewer products, other PDM e.g. IVIG will experience higher prices and hence developing countries will possibly face lower availability of PDM.

3. Current situation

It is clear that the economic status of nations directly influences quality of the care of patients in need of PDM including those with blood disorders. According to WFH in 2007 more than 5.2 billion IU of FVIII and about 475 million IU of FIX have been used worldwide. However, there is a considerable diversity in amounts of coagulating factors used in different countries. Per capita consumption of FVIII is directly influenced by the wealth of the nation. Although usage of 1 IU per capita coagulation factor could provide survival for hemophilia patients it is estimated that to live a normal life, these patients might require much higher factor usage, up to 5–7 IU per capita [9]. In 2007 per capita FVIII usage in countries with per capita GDP more than 10,000 USD was 3.47 IU which is 11 times more compared to countries with per capita GDP between 2000 and 10,000 USD and at least 173 times more than in countries with per capita GDP below 2000 USD [11]. However, there is a substantial increase in usage of FVIII both in developed and emerging economies. For example only in Russia since 2004 the total consumption of FVIII increased from 32 million IU to more than 463 million IU in 2008. consumption of FVIII increased from 32 million IU to more than 463 million IU in 2008.

Due to increased usage of recombinant FVIII (rFVIII), especially in developed economics, the share of rFVIII in the global market is increasing. Usage of rFVIII in the world shows a 163% increase while the increase for PD FVIII in only 15% [7]. Although until the mid 1990s PD FVIII was the driving product for plasma fractionators, the demand for recombinant coagulation factors VIII and IX especially in developed economies and increasing global demand for IVIG has now placed this product as the most important PDM. In 2007 about 82 tons of polyvalent IVIG are consumed worldwide [6]. Providing that prescription of IVIG remains limited to its current medical indications, it has been forecasted that IVIG usage would increase to about 120 tons in year 2012. However, there are some new indications for prescription of IVIG which obviously would dramatically increase the demand for this PDM in the coming years at least in developed economies.

Due to limited resources available for health care services in developing countries, patients in need of PDM should compete with much greater public health priorities such as primary health care, communicable and non-communicable disease and child care. Most governments in these countries spend less than 2% of their GDP on health care services. Spending on disease such as hemophilia or other "rare" disease in these countries is unlikely to become first priority. Therefore, patients with "rare" disease living in these countries might be totally ignored by their government. Due to high cost of PDM most patients, especially those who need chronic use of these medicines, would not be able to finance their needs. Therefore several countries both in developed and developing economies with established successful hemophilia care programs have implemented some sort of financial commitment from the government. However, in some countries subsidized or free factor concentrates are not distributed for home therapy but patients are required to visit a treatment center (mostly a designated one) for treatment of bleedings or prophylaxis [12].

4. Available options

Currently there are four options available responding to the needs of national health care systems for the PDM. These options are briefly discussed here.

4.1. Local production of PDMs

Local production of plasma either through blood banks (recovered plasma) and/or plasmapheresis (source plasma) creates the opportunity for local production of PDM. Although this seems lucrative, there are serious considerations surrounding this approach. In the past decades several countries both in developed and developing economies, in an attempt to reach self-sufficiency in PDM, have established local facilities for plasma fractionation. These facilities are mostly funded by governments. However, later due to concerns regarding cost-effectiveness of such facilities and more importantly, safety of products prepared, these facilities discontinued their activities. Later, developments in the field of transfusion have emphasized that the presence of an accountable national transfusion service is an essential component of any plasma collection and fractionation activities either as local production or contract fractionation activity. Therefore, self-sufficiency in plasma production depends heavily on the presence of an accountable blood transfusion service.

Local production of PDM could create the highest level of security for availability of PDM. However, this approach needs both a substantial investment and access to the knowhow for preparation of these medicines. Therefore only few countries, mostly developed countries, have pursued this option. Recently some countries in the developing world have also implemented long-term policies in plasma handling which may conclude in establishing a national facility for plasma fractionation. It is obvious that a viable local plasma fractionation facility could not only create the greatest degree of security for the availability of PDM for the national market but may also be taken as a sign of national pride in these countries.

Although lower cost of production of locally manufactured PDM is one major reason for promoting this option, it should be noted that mass production of some PDM especially factor concentrate by multi-national fractionators has substantially reduced the price of commercially available factor concentrates. This may reduce economic feasibility of establishing local fractionation facility.

4.2. Importation of PDM

Decision makers of national heath care system should decide whether to use the available resources for importation of PDM or investing in developing infrastructure for local production of such medicines. Importation of PDM and especially PD coagulating factors which are now available commercially at about 0.15–0.25 USD per IU could provide prompt access to these medicines. However, even with minimum factor use, treating one hemophilia patient will cost at least several thousands USD per year. Much higher costs attributed to treatment of patients in need of IVIG with current price of about 40–60 USD per gram, will impose significantly higher burden on both patient and national health care system.

Although importation of PDM, whenever resources are available, might look the easiest approach for availability of these medicines it could also create some serious problems. Worldwide shortage of these medicines and limited resources available in countries' health care system make this approach far from ideal. In case of global shortage most of the national authorities give priority to their own market and will put some restrictions on exportation of the medicine. Therefore, importing countries have to struggle to sustain availability of such products for their patients. On the other hand brand switching of imported PDM could also result in undesirable effects on patients and clinicians.

4.3. Contract fractionation

Another successful approach adopted by many countries both in developed and developing economies for provision of PDM is contract fractionation of locally produced plasma mainly in their national transfusion services. Plasma contract fractionation is a program in which local plasma is sent to the fractionator and end products are returned to the country of the plasma supplier.

Although plasma recovered from blood donations could be a main source for production of PDM, not meeting the standards imposed by the regulators is a major cause for discarding recovered plasma produced in transfusion services. Therefore any investment on national blood service quality assurance system for improving standards of the plasma recovered in blood centers could be considered a significant mean to improve national availability of PDM. Before implementation of a plasma fractionation program some operational changes in the national transfusion systems are necessary. Epidemiological surveillance of the donor selection, implementation of an information system, donor screening and traceability, validating blood/plasma collection, screening tests and plasma freezing and storage are among the most important aspects of a national program intending to produce plasma meeting the international standards. Obviously such operational improvements will have positive impacts on the quality and safety of blood components [13,14].

Before starting any contract fractionation activity, the economic balance of the whole program and its cost-effectiveness should be carefully evaluated. In order to do so, the main elements of cost contributing to such program should be taken into account. Some of the main elements include cost of plasma collection including donor recruitment, serology and NAT testing of donations, costs attributed to plasma storage, fractionation charge per unit of product made, shipment of the products back to the country of origin, plasma product registration, marketing/sales expenses and administration and overhead charges.

Following are the main advantages of a contract fractionation program [15,16]:

- improving national blood and/or plasma collection system through enforcement of standards required for plasma production to be suitable for fractionation;
- the source of the plasma and its level of quality is known;
- surplus of the recovered plasma produced in national transfusion system will not be wasted;
- provides a fairly rapid access to the PDM;
- provides a relatively secure approach for access to PDM even during global shortage of PDM;
- does not need capital investment;
- flexibility for selection of the fractionator.

However, before putting plasma contract fractionation on the table of a national health system it should be kept in mind that a reliable and well-organized national transfusion, preferably centralized system, should be in place and a real cost estimation should be considered. While negotiating with the fractionators to finalize the agreement, a range of topics including source of plasma supply, plasma volume, duration of the agreement, product profile and characteristics should be considered. This has been previously discussed in details [15,16]. Yield, particularly for IVIG is an important parameter and should be given close consideration while negotiating contract fractionation agreement.

A plan for collecting and transferring plasma produced in collection points across the country to the central warehouse should be arranged. A reliable cold chain for transferring plasma from collection centers throughout the country and its shipment to the fractionator site is mandatory for any contract fractionation plan. From both economic and logistic aspects, most likely transfer of large volume of the plasma for contract fractionation by airfreight to the fractionator site is not feasible. Therefore land and/or sea shipment are the most practical options. However, the fact that it may take several weeks to ship plasma consignments to the fractionator site, advanced planning is necessary in order to avoid any delay for receiving back produced PDM. Therefore, the return of produced PDM from fractionator site by airfreight should always be considered as the first option. This will significantly reduce the turnaround period between plasma shipment and availability of PDM produced from national plasma.

Contract fractionation could also create some difficulties. Any technical problems in the fractionator site might seriously impair national availability of PDM, if a contingency option is not in place. The activity may also create hostility from PDM importers and they may cause resistance toward prescription and use of produced

medicines through complaints of some physicians and patient groups.

Any contract fractionation activity should be evaluated periodically and its impact on affordability of PDM in national market assessed. Although several countries, both in developed and developing economies, are using the plasma contract fractionation approach to meet their national needs for the PDM, only few have reported its economical impacts on their health care system [13,17,18].

4.4. Combined approach

Availability of the PDM in the national market should be influenced by the clinical needs of the patient and not by the capacity of the contract or local fractionation project. Therefore many countries have adopted a combined approach to supply their national market with PDM. There are very few countries worldwide which are self-sufficient in plasma production and PDM. Therefore, combined approach including importation, local production and/or contract fractionation would be the most practical way for accessibility to PDM.

Although PDM market is currently dominated by multi-national fractionators based in developed economies there are still a few countries in the developing world which have a national plasma fractionation plant. However, these countries are still not self-sufficient and they either have to import some PDM or do not fully respond to the patients' needs to PDM.

5. Countries' experience

There are published reports that some countries in the developing world including South Africa, Cuba, Thailand and Brazil have established some kind of local production of factor concentrates and other PDM to support patients' needs [19]. However, local production of low cost PDM in these countries is not able to provide comprehensive care for the patients. Considering limited resources available in health care system of these countries it seems this might be the most cost effective use of the resources. Otherwise relying solely on importation of PDM might reduce number of patients who would have access to these medicines. The government of Thailand subsidizes major portion of the cost of treatment of hemophiliacs. However, commercial coagulating factor concentrates are not widely used because of their unaffordable prices. Hemophilia patients in Cuba are mainly depending on cryoprecipitate produced in blood banks for their treatment [12,19]. In addition to the published reports it seems that some other developing countries are also operating their national facilities for production of PDM. However, there might be some concerns regarding quality and safety of products manufactured in these facilities.

Brazil with a well-populated developing country and about 4 million whole blood donations could theoretically produce annually about 500,000 l of plasma for fractionation. However, it has been reported that only 200,000 l of this plasma fulfill the requirements for fractionation in fractionators based in a highly regulated country. The country has recently implemented a program for qualification of all 500,000 l of plasma produced in its national transfusion services for fractionation by the year 2012. Although Brazil still depends on importation of the PDM, since 2002 it has established a contract fractionation program [13].

Canada has a policy to collect apheresis plasma for transfusion purposes and therefore diverts all its recovered plasma produced in national blood centers for fractionation. Canadian Blood Services currently has contract fractionation agreement with two fractionators for fractionation of all recovered plasma produced in its centers into IVIG and albumin. Canada began plasma self-sufficiency program in 1998 and since then has established 18 plasma centers in 7 years. However, in 2009 the country was able to produce only 28% of its need to PDM including IVIG from Canadian plasma. Therefore, since self-sufficiency, defined as 100% of IVIG needs met from Canadian plasma would not seem practical, the country has abandoned long held belief in plasma self-sufficiency [20].

In Australia plasma collected by the national blood service from Australian donors is fractionated by a local fractionator. While the great majority of plasma products provided to the Australian community are manufactured from domestically sourced plasma, the importance of ensuring a secure and adequate supply of plasma derivatives, sufficient to meet the needs of all Australian patients, necessitated arrangements for the importation of some fractionated products. The critical factor in forecasts concerning future demand for plasma products in Australia is the projected demand for IVIG. Over the past decade, demand for IVIG in Australia has increased at an annual rate of 14%, a growth rate much higher than that for the supply of plasma available for fractionation. Therefore since 2003–2004 the domestic IVIG supply has been supplemented with imported products.

Forecast indicates that by 2015–2016 the level of demand for IVIG in Australia would be more than double the amount of current consumption of IVIG. At present rate of product yield, this would mean that the amount of raw plasma collected from Australian donors in 10 years' time must be more than double. It means that Australia will require 686 tons of starting plasma in 2015–2016, compared with 308 tons in 2005–2006, an increase of 123% in the decade [21].

6. Iran experience

Iran has the highest per capita consumption of FVIII in the East Mediterranean region. Although per capita GDP in Iran is reported less than 10,000 USD; consumption of FVIII in Iran (1.8 IU per capita) is almost five times higher than other countries with GDP per capita between 2000 and 10,000 USD [11]. Along with improvement of standards of care in Iran health care system, consumption of PDM steadily rose [22]. According to the statistics, costs of imported PDM accounts for more than 40% of the total value of imported medicines into Iran's pharmaceutical market [23]. This indicates a significant burden on limited resources available in the national health sector.

Following reports of HIV cases among the hemophilia patients throughout the world in the 1980s, due to some concerns regarding the efficiency of viral inactivation methods, Iran has ceased the production of clotting factors in its local fractionation facility. Therefore, in the past years Iran has decided to implement a contract manufacturing project to produce PDM from Iranian plasma produced in the country's centralized blood transfusion system.

In Iran, the blood transfusion service has evolved as a result of direct intervention of the government in the national health sector. In recent decades, a shift from whole blood use to component therapy resulted in the generation of surplus of recovered plasma from donated blood. This created an opportunity for Iran's health care system to use this plasma for production of PDM. Since about 1.8 millions blood donations from voluntary and non-remunerated donors are collected each year, Iran national transfusion service is able to devote substantial volume of plasma for fractionation. After responding to the needs for fresh plasma and cryoprecipitate, each year about 150,000 l of recovered plasma could be allocated to fractionation [24].

Table 2
Average annual usage (per 1000 population) of albumin, FVIII and IVIG in Iran and share of products produced from Iranian plasma during 2006–2008.

Product	Quantity	Share of local plasma
Albumin	113.1 g	18%
IVIG	6.3 g	46%
FVIII	1800 IU	6%

Since Iran's national transfusion system decided to collaborate with European fractionators [14], details of quality assurance and cold chain systems of blood collecting centers were inspected by the auditors of both European Regulatory Authorities and fractionators, before receiving the authorization of exporting plasma to Europe. Implementation of recommendations from auditors' reports played a substantial role in improving the quality assurance system in general, and especially in the plasma collection part [14].

Except for antihemophilic factors VIII and IX which are highly subsidized by the government and are nearly free of charge for patients with clotting deficiencies, cost of IVIG and albumin should be supported by either insurance companies or patient. Therefore PDM produced through the contract fractionation project at notably lower price than those of commercial products available on the market could play a major role in improving affordability of these medicines. In addition it provides a substantial saving of resources allocated to the importation of these medicines. Availability of medicines produced from Iranian plasma in the market (46% for IVIG and 18% for albumin; Table 2) has inevitably forced the international pharmaceutical companies to offer more reasonable prices for their products in order to hold their share of the Iranian market [18].

It is obvious that volume of recovered plasma collected in the national blood system is not enough to reach self-sufficiency. However, it should be kept in mind that creating a self-sufficiency of PDM on the basis of plasma collection from voluntary donors in the near future would be a difficult task to achieve. Irrespective of the interventions, national plasma production capacity should be improved in order to secure the availability of affordable PDM [18].

Currently decision makers in Iran's health care system are seriously considering establishing a domestic plasma fractionation facility. Therefore it is highly possible that Iran will build up its national fractionation capacity based on the latest GMP standards. However, until the project is completed, Iran will continue to use internationally available fractionation capacity especially in highly regulated countries for contract fractionation of recovered plasma produced in the national transfusion service. This activity might also continue as part of the technology transfer package for domestic fractionation facility at a later stage.

Acknowledgements

Authors wish to thank professor JP Allain for his valuable comments on the manuscript.

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