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ORIGINAL ARTICLE

# Economical impact of plasma fractionation project in Iran on affordability of plasma-derived medicines

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SUMMARY. In Iran all transfusion services are concentrated under authority of one public and centralized transfusion organization which has created the opportunity of using plasma produced in its blood centers for fractionation. In 2008 voluntary and non remunerated Iranian donors donated 1.8 million units of blood. This indicates a 25/1000 donation index. After responding to the needs for fresh plasma and cryoprecipitate each year about 150 000 L of recovered plasma are reserved for fractionation. In an attempt to improve both blood safety profile and availability and affordability of plasma derived medicines, Iran's national transfusion service has entered into a contract fractionation agreement for surplus of plasma produced from donated blood by voluntary non remunerated donors. In order to ensure safety of product produced, Iran has chosen to collaborate with international fractionators based in highly regulated countries. The main objective of this study was to evaluate the impact of contract plasma fractionation on the affordability of the plasma derived medicines in Iran. During 2006–2008, Iran's contract fractionation project was able to produce 46%, 18% and 6% of IVIG, Albumin and FVIII consumed in Iran's market, respectively. In contrary to IVIG and Albumin, due to fairly high consumption of FVIII in Iran, the role of fractionation project in meeting the needs to FVIII was not substantial. However, Iran's experience has shown that contract plasma fractionation, through direct and indirect effects on price of plasma derived medicines, could substantially improve availability and affordability of such products in national health care system.

*Key words*: affordability, contract plasma fractionation, Iran, national transfusion service, plasma-derived medicines.

Iran's health system has been substantially improved in recent decades. Currently, not only viable basic and public health facilities are freely accessible by the general population (Asadi-Lari *et al*., 2004), but also most of the highly specialized medical interventions are available to all Iranian patients in need of such treatments. Although Iran is still categorized as a developing country, patients with immunological and blood disorders (including hemophiliacs and thalassemics) receive medicines that are available to those patients in developed economies. It is obvious that the provision of packed red cells and concentrates of coagulation factors and immunoglobulins are essential components of a comprehensive care programme for these patients. Unfortunately, the high cost of these medicines has impeded their affordability for those living in low resourced countries. About 80% of hemophiliacs who are living in developing countries may not have access to sufficient amounts of concentrates of coagulation factors (Bird *et al*., 1998; Farrugia, 2004a). Cost of plasma-derived medicines, especially coagulation factors, is a substantial burden on Iran's health care sector. In order to reduce the price of medicines for patients, imported concentrates of clotting factors are heavily subsidized by Iranian government. Therefore, the availability of these medicines in Iran's pharmaceutical market depends mainly on the

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financial resources available in country's health sector. As the standards of medical care continue to rise in Iran, the country is experiencing an increase in demand and subsequently importing plasma-derived products, in spite of a steady increase in their prices (Cheraghali, 2007).

Currently, there are about 7000 patients with haemophilia in Iran (WFH, 2007) whose comprehensive care is supported by the national health system. It was previously reported that per capita consumption of antihemophilic factor VIII (FVIII) in Iran and the costs associated with it are substantially higher than what is expected for a country with GDP per capita less than 10 000 USD (Cheraghali, 2007). The increasing pressures due to the costs associated with prescription and use of plasma-derived medicines in Iran have forced Iranian health authorities to seek for alternatives to relieve the pressure. One practical way was that the country, instead of relying totally on imported plasma-derived medicines, considers the use of the plasma produced in the national transfusion system for fractionation. Since the establishment of fractionation facilities for local production of plasma-derived medicines in Iran, due to its financial and technical requirements, has not yet been fruitful, contract fractionation of plasma remained as a practical option (Cheraghali & Abolghasemi, 2009).

Although blood donation has been a tradition among human societies for a long time, innovation of Edwin Cohn for the fractionation of plasma and, later in 1964, the serendipitous discovery of cryoprecipitate which is rich in FVIII, von Willebrand factor and fibrinogen caused major advances in developing plasma-derived medicines. Since then, along with the improvement in plasma fractionation techniques and production of new derivatives, clinical use of these products has also increased dramatically. Today 23–28 million litres of human plasma are fractionated each year throughout the world of which about 35% is obtained from whole blood donation (recovered) and 65% by apheresis (Burnouf, 2007a). Nevertheless, the affordability of these medicines especially for patients living in developing countries is still a huge obstacle. Therefore, supply of coagulation factors and immunoglobulins at affordable prices and in sufficient quantities remains an important issue. Following the publication of reports regarding the transmission of viral pathogens through plasma-derived coagulation factors in past decades, prescription and use of recombinant factors in rich economies have substantially increased. However, development of inhibitors in patients using recombinant factors is still a concern and it is reported that plasma-derived FVIII products may even confer a lower risk to develop inhibitors than recombinant FVIII products in patients with severe haemophilia (Goudemand *et al*., 2006). Although in recent decades there is a significant shift towards using the recombinant factors in highly resourced countries, this in fact may lead to an increase in the mean price of plasma-derived FVIII in the developing countries (Burnouf, 2007a).

It should be noted that the price of plasma-derived medicines is very much influenced by the price of plasma as the raw material. Therefore, the use of plasma, produced as a by-product of blood donation through mainstream transfusion services, appears to be a logical option for the supply of plasma derivatives. The fact that since 1974 all blood transfusion services in Iran have been organized under one single centralized public blood transfusion organization that oversees all blood transfusion activities from donor recruitment to production and delivery of blood and blood components, has created an opportunity of using the plasma produced in these centres for fractionation. In Iran, blood transfusion is an integral part of the national health system. In order to meet the country's demand, in 2008 Iranian Blood Transfusion Organization (IBTO) collected more than 1·8 million units of blood from 100% voluntary and non-remunerated donors in a country with a population of over 70 millions. This has created self-sufficiency for whole blood and the components (Abolghasemi *et al*., 2009). This is a general consensus that a national blood service plays a crucial role in providing safe and adequate plasma for fractionation and production of coagulation factors, albumin and immunoglobulins (WHO, 2005).

Although IBTO started the plasma fractionation process to respond to the clinical needs of patients with blood disorders in 1970s, an affiliated company named Iranian Blood Research and Fractionation Company (IBRF) was then established with the capacity of fractionating over 80 000 L plasma per year. However, due to some concerns regarding the efficiency of viral inactivation methods and techniques used in this facility, Iran's National Regulatory Authority (NRA) asked IBRF to stop the production of plasma derived coagulating factors in its fractionation facilities in 1990s. Therefore, since 2005, a contract fractionation project for the surplus recovered plasma produced in IBTO has been started. Although improving the blood safety profile of the country through improving quality assurance system, epidemiologic surveillance of the donor population, donor deferral policies and screening practices and mandatory donation testing has been one of the main objectives of this project, the activity has also significantly improved availability of plasma-derived medicines in the country (Cheraghali & Abolghasemi, 2009). Because IBRF is a non-profit company, it is expected that the plasma-derived medicines produced

through this project should have lower prices compared with those that are commercially available in the market. Therefore, both national health system and patients receiving these medicines would be the main beneficiaries of this vital project. The objective of this paper is to demonstrate the economical impact of Iran's plasma fractionation project on the availability and affordability of the plasma-derived medicines in Iran market.

## ECONOMICAL IMPACT OF THE PROJECT

During 2006–2008, IBRF on average exported about 75 000 L plasma to the fractionator annually. Obviously the medicines produced from this volume of plasma played a critical role in providing necessary medicines to Iranian patients. Due to internal administrative and budgetary regulatory requirements, IBRF has used an annual-based tender system for contract fractionation. However, only European-based fractionators who already had registered their plasma-derived products in Iran's NRA were entitled to participate in the tender. The annual-based tender approach, due to audits and inspection requirements by new fractionator, could potentially create delay in implementation of the contract. However, since during past 4 years one specific European-based company was the winner of the IBRF 's tenders these problems have been avoided.

Plasma is a very valuable raw material and should be converted to as much medicines as practically possible. It has been reported that the cost of 1 L plasma, meeting the requirements for fractionation, is worth between 60 and 100 Euros. Therefore, cost of raw material plays a major role in final cost of plasma-derived medicines. Considering the impact of the cost of 1 L plasma on the price of intravenous immunoglobulin (IVIG), albumin, FVIII and factor IX as the major products obtained with an allocation of 40, 25, 25 and 10%, respectively, it is expected that each 10 Euro increase per litre of plasma will result in an increase of 0·1 Euro per gram of albumin, 1 Euro per gram of IVIG and about 1·6 Euros per 100 IU of FVIII (Burnouf, 2005–2006). However, it should be mentioned that the final price of the products is directly dependent upon product yield per litre of plasma and this should be considered while calculating such incremental costs.

Therefore, the production yield was one of the major considerations for IBRF when negotiating with fractionators. IBRF has requested the fractionator to guarantee a minimum production yield per litre of plasma at least for three major products (IVIG, albumin and FVIII), produced from delivered Iranian plasma. The range of production yield for 1 L of delivered Iranian plasma to the fractionator is summarized in Table 1.

**Table 1.** Range of production yield of plasma-derived medicines from 1 L of Iranian plasma

| Product | Final production yield |
|---|---|
| Albumin | 22·3–26·0 (g/L) |
| IVIG | 4·2–4·6 (g/L) |
| FVIII | 142·4–153·2 (IU/L) |

It was found that the yield for IVIG and albumin was within expectations but for FVIII it was less than that found for plasma from European sources fractionated by the fractionator. Further investigation on Iranian plasma delivered to the fractionator revealed the lower content of FVIII compared with the plasma from European sources. However, the production recovery of FVIII from cryoprecipitate for both types of plasma was similar. On average, FVIII content of Iranian plasma on arrival to the fractionator was (6·8 IU/dL) lower than that of German sources (9·6 IU/dL). However, recovery percentage of FVIII in final product was not different for Iranian plasma (58·2%) and German source (54·6%). This indicates that Iranian plasma loses some of its FVIII during separation, storage and/or transportation processes. Further investigation is needed to pin point critical points leading to the loss of FVIII in plasma collected in IBTO blood collection centers.

As illustrated in Fig. 1, during 2006–2008 IBRF contract fractionation project was succeeded to produce 46, 18 and 6% of IVIG, Albumin and FVIII consumed in Iran's market, respectively. On average annual country consumption rates of IVIG, Albumin and FVIII during 2006–2008 were 6 kg, 113 kg and 2 MIU per one million populations, respectively. Considering the

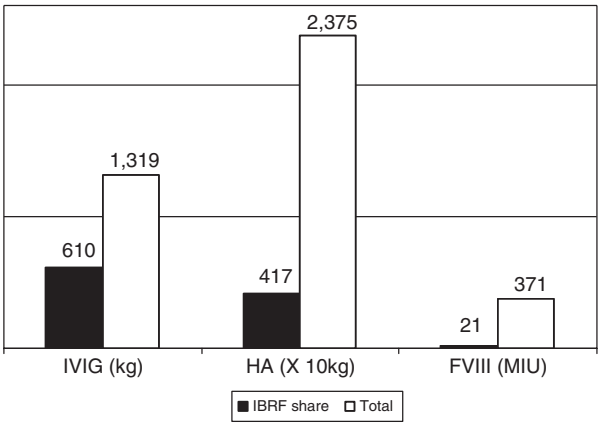


**Fig. 1.** Plasma-derived medicines consumed in Iran during 2006–2008 and the share of medicines produced from Iranian plasma through IBRF contract fractionation project.

 

status of IVIG as the driving force for the plasma fractionation, it is obvious that, in general, this activity has improved the availability of plasma-derived medicines for Iranian patients who need such medicines. Although the production yield for FVIII was in acceptable range (Table 1), due to fairly high consumption in Iran, the amounts of FVIII produced through the fractionation project have not been sufficient yet to reduce the need for importing of this drug. Therefore, as it is depicted in Fig. 1, the dependency of Iran's market to the imported plasma-derived medicines is still fairly high.

## DISCUSSION

Plasma-derived medicines have critical role in today's medicine. Currently, about 20 different plasma protein therapeutics are in the market and used for treating the life-threatening diseases or injuries associated to bleeding and thrombotic disorders, immunological diseases, infectious conditions as well as tissue-degenerating diseases (Burnouf, 2007a). Some of these medicines including immunoglobulins and coagulation factors are even included in the *WHO Model List of Essential Medicines*, reflecting the international consensus of their importance in treating life-threatening diseases. However, it should not be forgotten that plasma protein therapies are expensive and considerably inaccessible to the patients living in countries with limited resources available to the health sector (Srivastava, 2001). Therefore, economic status of the nations will influence the distribution and usage of therapeutic products. The trend towards the use of recombinant coagulation factors in the wealthy countries has continued to increase. However, financial constraints will impede the access to these products in developing countries. Recognizing that 80% of people with haemophilia are living in developing countries, it becomes clear that the delivery of the plasma-derived antihemophilic factors will be the main therapeutic option available in the developing world for the times to come.

It seems that the tendency of rich countries towards the use of the recombinant antihemophilic factors is likely to diminish the economical interest for the manufacturing of plasma-derived FVIII that remains a major option for hemophiliacs in developing countries. It is believed that the assumption that decreased use of plasma-derived FVIII or FIX in developed countries would increase the supply of products to developing countries may not be economically viable (Burnouf, 2007a).

Due to the improvement of standards of care, consumption of plasma-derived medicines in Iran shows a steady rise. According to the statistics reported by the Department of Pharmaceutical Affairs of Iran's Ministry of Health, costs of imported plasma-derived medicines account for more than 40% of total value of imported medicines into Iran's pharmaceutical market. This indicates a significant burden on limited resources available in national health care system.

Following reports of HIV cases among the patients with haemophilia throughout the world in 1980s, due to some concerns regarding the efficiency of viral inactivation methods used in the IBRF facilities, Iran NRA asked IBRF to stop the production of clotting factors in its fractionation facility until a validated viral inactivation technology is implemented. However, the decision to simultaneously expand the production facilities and implement a virus inactivation section has ceased the production activity since 2002 in IBRF. For this reason, it was decided to perform the contract manufacturing project to produce plasma-derived medicines from Iranian plasma until the new facility is erected.

Although, for countries without national fractionation capacity, importing these medicines might be considered as a prompt approach to furnish national market, worldwide shortage of these medicines and limited resources available in countries' health care system make this approach far from ideal. Therefore, contract fractionation projects for the production of these medicines remain a practical approach to respond to the needs of patients and physicians to these medicines. However, steady production of sufficient quantities of plasma either through plasmapheresis or donated blood is an essential prerequisite for any successful contract fractionation of plasma. This might be feasible in countries with an accountable national blood services. Such organizations that receive sufficient blood donation through non-remunerated donors could provide substantial quantities of safe plasma to be fractionated to its derivatives. Iran, as a country faced with increasing demand for plasma-derived medicines which lacks national fractionation capacity, relies on its centralized blood transfusion system for producing plasma for fractionation. Iran has successfully implemented this approach in past years to improve availability and affordability of these medicines.

Following the introduction of improved methods for blood/plasma donation screening and processing, GMP principles and associated regulations, the quality and safety of blood and plasma collected in developed countries have dramatically improved. In contrast, comparable levels of quality, safety and availability do not exist in most developing countries, where the potentially available plasma for manufacturing the related products does not meet the necessary quality standards and therefore it is destroyed. Hence, patients in these countries do not have sufficient access to these

 

essential medicines. Although it is reported that over 23–28 million litres of plasma are fractionated each year in the world and about 35% of these amounts of plasma are collected from recovered plasma, it is estimated that at least 5·8 million litres of recovered plasma are destroyed, mainly in the developing countries (Burnouf, 2007b). Recently, WHO has announced the initiation of the 'Achilles' project in developing countries. This project seeks to increase the availability of safe plasma-derived products for developing countries through supporting the implementation of national validated quality and safety standards for blood establishments and enables them to produce qualified human plasma for fractionation (WHO, 2008).

In Iran, blood transfusion service has been evolved as a result of direct intervention of the government in national health sector. In recent decades, a shift from whole blood use to components therapy has resulted in the generation of surplus of recovered plasma from donated blood. This created a good opportunity for Iran's health care system to use this plasma for production of plasma-derived medicines. Each year about 1.8 millions blood donations from voluntary and non-remunerated donors are collected. Therefore, IBTO is able to produce about 250 000 L plasma annually. After responding to the needs for fresh plasma and cryoprecipitate, each year about 150 000 L of recovered plasma could be reserved for fractionation (Abolghasemi *et al*., 2009).

Since Iran's national transfusion system decided to collaborate with European fractionators (Cheraghali & Abolghasemi, 2009), details of quality assurance and cold chain systems of blood collecting centres of IBTO were inspected by the auditors of both European Regulatory Authorities and fractionators, before receiving authorization for exporting plasma to Europe. Implementation of recommendations from auditors' reports has played a substantial role in improving the quality assurance system in IBTO in general and more especially in plasma collection part. In order to transfer plasma collected in blood centres throughout the country, IBRF has established a validated transport system including refrigerated trucks. Transported plasma is stored in a central warehouse in IBRF and following final release by QA department is shipped to the fractionator site. According to the fractionation agreement, the fractionator should also perform Nucleic Acid Testing (NAT) for HCV, HBV, HIV, HAV and parvovirus B19, on every unit of the plasma (through minipools) exported for fractionation. The fractionator is obliged to notify IBTO of any positive or indeterminate NAT results performed on plasma units for look back purposes (Cheraghali & Abolghasemi, 2009).

In contrary to blood and blood components which are currently provided free of charge for all Iranian patients, plasma-derived medicines in Iran are regarded as medicines and should be paid for (Cheraghali, 2007). Except for antihemophilic factors VIII and IX that are highly subsidized by the government and are free of charge for patients with blood disorders, cost of immunoglobulin and albumin should be born by either insurance companies or the patient. IBRF is a non-profitable governmental company that has to recover its operational costs through products and services provided. Therefore, the price of the plasma-derived medicines distributed by IBRF consists of the costs for plasma preparation from donated bloods, its transportation and fractionation and the operational costs of the company. As expected, the price of plasma-derived medicines prepared by IBRF is notably lower than those of commercially products available in the market. Although several countries, both in developed and developing economies, are using plasma contract fractionation approach to meet their national market needs for the plasma-derived medicines, only few have reported its economical impacts on their health care system (Flesland *et al*., 2003; Farrugia *et al*., 2009). Price of the plasma-derived medicines produced through IBRF contract fractionation on average is at least 15% lower than that of the commercial products available in the Iran market. This obviously indicates substantial savings for public health budget. However, in addition to substantial direct effect of this project on saving of resources allocated for importation of these medicines, indirect influence of the IBRF project on reducing costs of imported commercial medicines is more pronounced. Availability of medicines produced from Iranian plasma in the market (46% for IVIG and 18% for albumin; Fig. 1) has inevitably forced the international pharmaceutical companies to offer more reasonable prices for their products in order to hold their shares in Iran's market. In fact, the presence of the products produced from contract fractionation in the market, through improving bargaining power of the national authorities on commercial products, has contributed greatly to maintain a downward pressure on the price of the commercially available plasma-derived medicines in Iran market.

It is obvious that volume of recovered plasma collected in IBTO is not enough to create self-sufficiency for the country. Therefore, Iranian authorities are planning to increase the volume of domestically produced plasma. Obviously, due to both ethical issues involved in discarding donated components and also due to safety factors involved, IBTO is not intended to increase blood collection solely for increasing plasma production. However, collection of source plasma by

 

apheresis has the potential to generate sufficiency in plasma products without affecting the logistics of mainstream blood components.

The experience in the developed world is that intensive plasma collection as generated through the commercial plasma sector has proven to be unattainable in the voluntary donor system at least to the level of self-sufficiency (Farrugia, 2004b). Although the plasmapheresis is an alternative for Iran to increase the volume of plasma produced, one should keep this in mind that creating a self-sufficiency of plasma-derived medicines on the basis of plasma collection from voluntary donors in near future might be a difficult task to achieve. This is mainly because currently Iranian donors, as an altruistic contribution to the society, would like to donate their blood and not watery plasma! Therefore, an implementation of a long-term and multi approach policy is needed in order to encourage Iranian volunteers to donate both whole blood and the blood components (i.e. plasma) as a contribution to their society. Irrespective of the interventions, national plasma production capacity should be improved as a means for securing availability of affordable plasma-derived medicines.

Although the established fractionation facilities in the developed world currently have an over capacity which could be used by the developing countries and despite the fact that establishing a domestic plasma fractionation facility is a resource intensive practice, decision makers in Iran's health care system are seriously considering this approach. For several reasons, the benefits of having a number of well-resourced plants in the developing world appear to make this option attractive (Srivastava, 2001; Farrugia, 2004a). Therefore, it is highly possible that Iran will build up its national fractionation capacity based on the latest GMP standards. However, by the time the project is materialized, Iran will continue to use internationally available fractionation capacity especially in highly regulated countries for contract fractionation of the recovered plasma produced in its national transfusion service. This activity might also continue as part of the technology transfer package for domestic fractionation facility in a later stage.

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