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Original Article

# Plasma Production in Iran: Streaming Towards Plasma Self-sufficiency

Zahra Ghasemi [1], Hassan Abolghasemi [2], Fatemeh Babaei [1], Abdol Majid Cheraghali [3], Nazila Yousefi [4*]

[1] Department of Pharmacoeconomics and Pharma Management, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Pediatric Congenital Hematologic Disorders Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Professor of Pharmacology, Board member of Iranian Academy of Medical Sciences, Iranian Academy of Medical Sciences, Tehran, Iran
[4] Department of Pharmacoeconomics and Pharma Management, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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## Abstract

**Introduction:** The role of Plasma-Derived Medicinal Products (PDMPs) in managing life-threatening diseases is remarkable. Human plasma as a raw material for PDMPs is obtained from volunteers through apheresis or whole blood collection. The global PDMPs market in 2021 shows an average annual growth rate of 7.4% since 1996 which is higher than the average annual pharmaceutical market growth rate. In line with WHO policies, Iran has improved its national voluntary non-remunerated donors (VNRD) program to supply the local PDMPs market. This study shows the 10-year Iran PDMPs market evolution to assess its self-sufficiency.

**Method:** We conducted a cross-sectional study from 2012 to 2021 to assess the self-sufficiency rate of Iran's plasma industry for PDMPs including Albumin, Immune globulins, and Antihemophilic Factors. In addition, we show the gap between market supply and demand to lighten the self-sufficiency future.

**Result:** The annual growth rate of total collected plasma was 18.9% over 10 years in Iran from 2012 to 2021. Although the consumption rate of intravenous Immune globulins has increased from 777 kg to 2,108 Kg, due to a significant increase in local plasma production, its self-sufficiency rate increased from 53% to 93%. Similarly, the self-sufficiency ratefor Albumin grew from 21% in 2012 to 90% in 2021.

**Discussion:** Although local plasma production in Iran significantly provided plasma self-sufficiency as a raw material, local market demand for PDMPs is mainly supplied through contract fractionation with European fractionators. Access to complete self-sufficiency in Iran needs increasing plasma production, as well as developing major local plasma fractionators.

* Corresponding Author:
**Nazila Yousefi**
Affiliation: Department of Pharmacoeconomics and Pharma Management, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran
E-mail: **n.yousefi@sbmu.ac.ir**



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## 1. INTRODUCTION

Plasma-derived medicinal products (PDMPs) are vital in prophylaxis and managing life-threatening conditions, like hemophilia, autoimmune diseases, acquired and congenital immunodeficiency, and other protein disorders (1). PDMPs including Albumin, Immunoglobulins (Igs), Antihemophilic factors, and other plasm proteins built an innovative approach to the treatment of important diseases (2) and are listed as essential medicines by the World Health Organization (WHO) (3).

The most abundant components of plasma that serve as market drivers for PDMPs are Albumin and Immune globulins (4). Albumin is widely used for the treatment of burns, blood losses, trauma, hemodialysis, resuscitation, hyperproteinemia, hemorrhage, cardiopulmonary bypass, and acute respiratory distress syndrome (5). Ig products are used to treat patients across a broad spectrum of diseases such as primary and secondary immunodeficiency, immune thrombocytopenia, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, Kawasaki disease, multifocal motor neuropathy, chronic inflammatory demyelinating poly-radiculoneuropathy, and so forth (6).

Human plasma, the raw material for producing plasma-derived medicines is obtained by donation of individual volunteers mostly by apheresis method, called source plasma. The remaining portion is extracted from whole blood called recovered plasma (7). WHO emphasizes each country should implement national donor criteria and screening policies, according to the latest epidemiology of local infections in the country, to prevent inter-region transfusion-transmissible infections. Moreover, it has been encouraged that local plasma be collected in order to produce plasma-derived medicines due to the notable variations in blood-borne infections and the significant discrepancies in the prevalence of these infections in each origin. In this line, national programs and efforts in Iran have been made to use Iranian plasma to prepare plasma-derived medicines to enhance both the accessibility and safety of PDMPs (8,9). Supplying PDMPs from local plasma, even toll manufacturing, not only provides safer and more effective medicines (as in the case of normal immunoglobulin) but also provides less expensive products particularly compared to imported commercial ones (10).

Until 2007, around 25 million liters of plasma were fractionated annually in approximately 70 fractionation plants worldwide, with a 69-million-liter increase by 2019. Although it experienced a 14% decrease due to the COVID-19 pandemic and reached 59 million liters in 2020, it increased again to around 62 million liters in 2021.

According to the reported data at the International Plasma Protein Congress in 2022, the Marketing Research Bureau (MRB) declares a 7.4% annual growth rate in PDMPs worldwide from 1996 to 2020, ranging from 4.8 billion USD to 26.6 billion USD, with intravenous and subcutaneous Immune globulins accounting for the highest share (11,12).

From the global point of view, recovered plasma is mainly obtained by government-owned centers, and source plasma is obtained by private centers with a capacity ranging from 50,000 to 3 M liters. However, due to the complexity of plasma fractionation, the plasma industry has gone through an acquisition or contract strategy to fractionate PDMPs from human plasma (12).

## 2. PLASMA PRODUCTION AND FRACTIONATION IN IRAN

Iran is a developing country located in western Asia with an advanced healthcare system in which around 8% of its gross domestic production (GDP) belongs to health (13).

PDMPs are listed in the official Iran drug list and blood transfusion and plasma-derived therapies are an integral part of Iran's national health system; in a way that in 2021, the share of PDMPs value was around 24% of total imported pharmaceutical medicines (14). The national blood transfusion system is governed by the Iranian Blood Transfusion Organization (IBTO) established in 1974 by the government and started the activities regarding blood donation by increasing the number of voluntary non-remunerated blood donations all over the country (15). In 2007, by improving the governmental system and establishing private plasma centers, Iran reached the top rank of blood and plasma transfusion systems in the Middle East region (13). In 2019, Iran cumulate collection of governmental (38%) and private sectors (62%) reached 450 thousand liters plasma which was 33% of the total collected plasma in the Middle East and African region. Moreover, Iranian plasma collection centers achieved high-quality standards, in a way that all are certified by European health authorities including AGES and Paul Ehrlich Institute with every 2-year follow-up inspection. In addition, they were periodically audited by the Iranian Food and Drug Administration (IRFDA), IBTO, and contracted fractionators (15).

IBTO share in collecting plasma was 40%, recovered, and the private sector share was 60%, source plasma, in 2021 (16). As



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the local production of plasma-derived medicines in Iran is limited, they are mainly supplied by importation. However, some under-construction programs for local manufacturing and a complete value chain are forthcoming (17). Iran had a historical experience of local fractionation in the governmental establishment. In 1994, IBTO owned the first plasma fractionation plant but due to economic burdens and lack of inefficient viral removal methods the project was shut down in February 1998 and surplus recovered plasma was discarded in 2001(13,18) since then, the supply of PDMPs has become highly dependent on the importation of finished products that some of them produced from Iranian plasma (19).

In the last decades, private companies developed up to 10 source plasma collection centers in Iran's high-populated cities to obtain enough plasma to completely cover patients' PDMP needs with local plasma. In 2020, around 490-thousand-liter plasma from both recovered and source types was sent to European fractionators for contract production of PDMPs that experienced 18.9% compounded annual growth for 10 years.

In this study, we attempt to evaluate data on locally acquired plasma for supplying PDMPs and investigate Iran's predicted future toward self-sufficiency.

## 3. METHOD

The following steps have been taken to analyze Iran's PDMP self-sufficiency potential:

1- We conducted a cross-sectional study from 2012 to 2021 using Excel 2019 software for the calculation of the market size (Million International Units for Factor VIII and Factor IX, and kg for IVIG and Albumin) for the four main PDMP products (Immunoglobulins, Albumin, Factor VIII, and Factor IX). The measures of the market volume of both imported and locally manufactured products are based on the official datasheets published by IRFDA.

2- Then, according to the calculated market size for each product and using the average yield (20) of fractionators, a calculation of the needed plasma for the supplied whole market demand has been conducted.

3- Finally, we showed the gap between market PDMPs demand and local plasma supply to self-sufficiency.

## 4. RESULT

According to the PDMPs' consumption and plasma fractionation yield, Iran needed about 600 thousand liters plasma to supply all PDMPs needs and fulfill health care demands in 2012. Though 103,290 liters were collected from all active centers in the mentioned year, the self-sufficiency rate of the main and critical product, IVIG, was 53% in 2012 which increased to 93% in 2021.

In 2012, 11,152 kg Albumin was used, with considering 100% fractionation yield of locally collected plasma, only 21% of the market needs had been covered.

Regarding Antihemophilic factors, all the patients' needs for plasma-derived Factors VIII and IX were covered through local plasma, and due to introducing domestic recombinant factors to the Iran market in 2015, and decreasing the total need for plasma-derived Factor VIII, the plasma in this case was more than local need.

The data regarding self-sufficiency in 2012, are summarized in **Table 1** (plasma production, product demand, and rate of self-sufficiency).

Building up the new plasma collection centers during studied 10 years, as well as increasing the collected volume of plasma in each center, resulted higher supply in 2021 as shown in Error! Reference source not found..

Self-sufficiency varies throughout PDMPs since each one has a varied extraction yield and a variable market demand. Additional details regarding Iran's four main PDMPs are provided below.

### 4.1. Intravenous Immunoglobins (IVIG)

The growing indications of IVIG, including labeled and off-labeled, have led to an incremental consumption rate of this product over the years all over the world. In a 10-year assessment (Figure 1), the average yearly growth rate of IVIG consumption in Iran was 29% (777 Kg in 2012 and 2,108 Kg in 2021) with an increasing growth rate. The COVID-19 pandemic's expansion in 2019 caused a 14% drop in the world's plasma collection, which in turn caused a decline in IVIG supply and following consumption (21). Concurrently, there was a growing need for IVIG despite the debatable evidence of its efficacy in treating COVID-19 patients, which prompted calls for the expansion of plasmapheresis centers across the globe followed by an increased rate of IVIG consumption (22).

The upward trend in the usage of IVIG in Iran is due to an increase in both labeled and off-labeled indications as mentioned in some recently published articles (23,24).

Based on the retrospective data and considering the average yield of 4-gram Ig per liter of plasma, the current plasma production was insufficient to cover the total demands in 2012 and only covered 53% of Ig demand. However, due to government policies regarding the development of private plasma collection centers all over the country and escalating the total collected plasma, Iran



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**Table 1.** Balance between supply and demand of local plasma- 2012

| Products | Theoretical yield per L | Demand | Plasma needed | Collected plasma | With the assumption of 100% fractionation | Self-sufficiency rate |
|---|---|---|---|---|---|---|
| IVIG | 4 g | 777 kg | 194,303 L | 103,290 L | 413 kg | 53% |
| Albumin | 23 g | 11,152 kg | 484,877 L | | 2,376 kg | 21% |
| p-Factor VIII | 220 IU | 138 M IU | 627,995 L | | 23 M IU | 16% |
| Factor IX | 100 IU | 23 M IU | 227,370 L | | 10 M IU | 45% |

**Table 2.** Balance between supply and demand of local plasma- 2021

| Products | Theoretical yield per L | Demand | Plasma needed | Collected plasma | With the assumption of 100% fractionation | Self-sufficiency rate |
|---|---|---|---|---|---|---|
| IVIG | 4 g | 2,108 kg | 527,101 L | 490,000 L | 1,960 kg | 93% |
| Albumin | 23 g | 12,571 kg | 546,550 L | | 11,270 kg | 90% |
| p-Factor VIII | 220 IU | 79 M IU | 360,692 L | | 108 M IU | 136% |
| Factor IX | 100 IU | 30 M IU | 302,620 L | | 49 M IU | 162% |


**Figure 1.** 10-year overview of IVIG consumption in Iran (Kg)

verged into more supply of local plasma for the PDMPs market and reached about 93% self-sufficiency rate of Immunoglobulins in 2021.

### 4.2. Albumin

Albumin is one of the PDMPs that is considered for its inappropriate consumption for several clinical conditions and its relatively high usage in hospitalized patients (25). The total demand for Albumin in 2012 was around 11 million Kg which raised to about 12.5 million Kg in 2021. The average growth rate of Albumin administration in the 10 years shows a 6% growth rate, which is lower than the immunoglobulin growth rate (**Figure 2**).

Considering the average yield of 23-gram Albumin per liter of plasma, in 2012, potential self-sufficiency for Albumin was 21% and it had boosted to 90% in 2021.

### 4.3. Antihemophilic factors

Antihemophilic factors are crucial and lifesaving for those patients with inherited rare X-linked bleeding disorders caused by mutations in the genes encoding coagulation Factor VIII and Factor IX respectively (26). With advancing diagnosis procedures in Iran, the number of these patients is increasing and according to the reported data by the Iranian Hemophilia Society, 1154 patients with hemophilia B and 5474 patients with hemophilia A were living in Iran in 2020. According to the reported data by the Plasma Protein Therapeutic Association (PPTA), the life expectancy of patients born with hemophilia reached 77 years in 2017, which was 13 years in the 1900s (27). In the following paragraphs, we will describe more about two main Antihemophilic factors in the Iranian market.



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### 4.4. Coagulation Factor VIII

Hemophilic patients in Iran, benefit from both plasma-derived and recombinant forms of Factor VIII. In early 2016, the importation of recombinant formulation was started and in parallel, one of the local manufacturers launched the first recombinant Factor VIII to the market. Since then, the local manufacturer has succeeded in covering 100% of the total recombinant needs of patients which according to the current treatment protocol, is about 70% of total consumption. So, the share of plasma-derived Factor VIII declined to 30% as shown in **Table 3**.

### 4.5. Coagulation Factor IX

Antihemophilic Factor IX was discovered in the late 1960s (28). Factor IX complex and its components are obtained from the supernatant of Cohn's Fraction or cryoprecipitate which undergoes several chromatography steps to achieve higher purity (29). The yield of Factor IX is inconstant and highly depends on the fractionation method but in general, from each liter of plasma 250 to 300 international units could be extracted (28).

Factor IX is one of the most important plasma-derived medicines and its production has an outstanding position due to the increasing need of patients. Factor IX is indicated for the treatment of hemophilia B patients, caused by a defective gene located on the X chromosome.

In Iran, Factor IX is completely supplied by contract manufacturing (9) and sourced from Iranian human plasma. The consumption trend of plasma-derived Factor IX is shown below (figure 4) and its average consumption unit in the past 10 years was 24 million international units.

## 5. DISCUSSION

Based on reported key facts by WHO, only 56 of 171 reporting countries produce PDMPs through the fractionation of plasma collected in the reporting countries and the volume of plasma for fractionation per 1000 population varied considerably between the 45 reporting countries, ranging from 0.1 to 52.6 liters, with a median of 5.2 liters. This plasma volume for fractionation declined at a rate of 14% in 2019 due to the COVID-19 pandemic and for preventing PDMPs shortages, aggressive strategies have been pursued mainly in the United States regarding heightening the plasma collection center numbers, which shows a 24% growth rate until 2021 (11,30).

The dependency of the plasma industry on human plasma as the raw material for manufacturing is not negligible and due to the lack of appropriate alternative solutions, maintaining the plasma industry is an integral part of the health care system in countries. As health structures improve and treatment protocols get complex, the stability in the supply of plasma-derived medicines becomes more crucial.

In lower to middle-income countries due to the insufficient volume of recovered plasma, the supply of high-quality PDMPs is under optimum level; but in developed countries like Italy, a development plan to collect more plasma through apheresis method and manufacture more PDMPs is among their health care plan priorities. In Italy, the achievement of self-sufficiency of PDMPs is set as a goal of the Italian blood system and the National Health Service to guarantee fair access to safe and high-quality products (31). Although Iran has a similar plasma industry in toll fractionation and plasma donation programs, the national plasma strategy for developing a future road map is missing in Iran

In line with the WHO guidance, the Italian Transfusion System put the self-sufficiency strategy among their top priorities to enhance access and supply of blood components and PDMPs. In the past two years, clinical needs for the administration of immunoglobulins increased and European countries by force dropped their way toward self-sufficiency (32). Since 2011, the demand for IVIG has been increasing in Italy, and it has lately been expanded to include subcutaneous Ig injections. Although implementing the national program in Italy to reach self-sufficiency in PDMPs during 2016-2020 (31) and establishing four companies performing toll manufacturing improved the production volume and access to PDMPs in 2019; still it is assumed that an estimated one million kg of national plasma for fractionation (for about 60 million inhabitants) won't be enough for Italy to be self-sufficient in Ig (33).

Albumin has a slower growth rate than Immunoglobulins worldwide. However, in Italy, clinical restrictions have been implemented by health authorities to manage inappropriate use of Albumin. Therefore, local programs for enhancement of plasma collection and toll fractionations lead to reach 95% self-sufficiency for Albumin in 2019(33). The growth rate of Albumin usage and reaching self-sufficiency in Iran had a similar trend to Italy; clinical usage of Albumin increased with a 6% annual growth rate for 10 years and enhancement of source plasma collection led to reaching 90% self-sufficiency.

For Antihemophilic agents, the global need for plasma-derived Factor VIII and Factor IX has declined since the recombinant formulations and non-factor alternatives evolved (34,35). In Italy, with emerging the new RNA-based interference technologies and aptamers it is estimated that p-Factor VIII and p-Factor IX won't be the top treatment option (33).

According to Iran's law and pharmaceutical policies, local manufacturers are supported by the government. In addition, self-sufficiency in the supply of plasma-derived medicines is a national goal in line with WHO



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**Table 3.** 10-year market of p-Factor VIII and r-Factor VIII

| Year | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 |
|---|---|---|---|---|---|---|---|---|---|---|
| r-Factor VIII (M IU) | - | - | - | 4 | 6 | 33 | 76 | 111 | 131 | 182 |
| p-Factor VIII (M IU) | 138 | 160 | 153 | 160 | 229 | 185 | 31 | 39 | 64 | 79 |
| Ratio (p/r) | 100% | 100% | 100% | 98% | 97% | 85% | 29% | 26% | 33% | 30% |

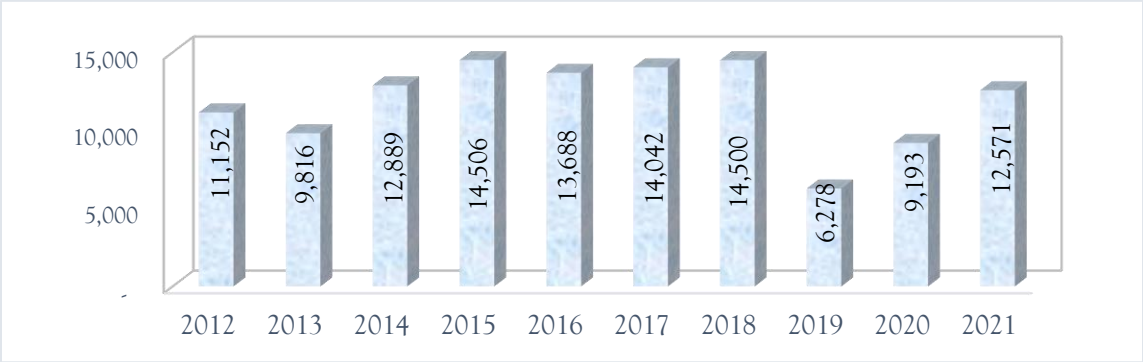


**Figure 2.** 10-year overview of Albumin consumption in Iran (Kg)

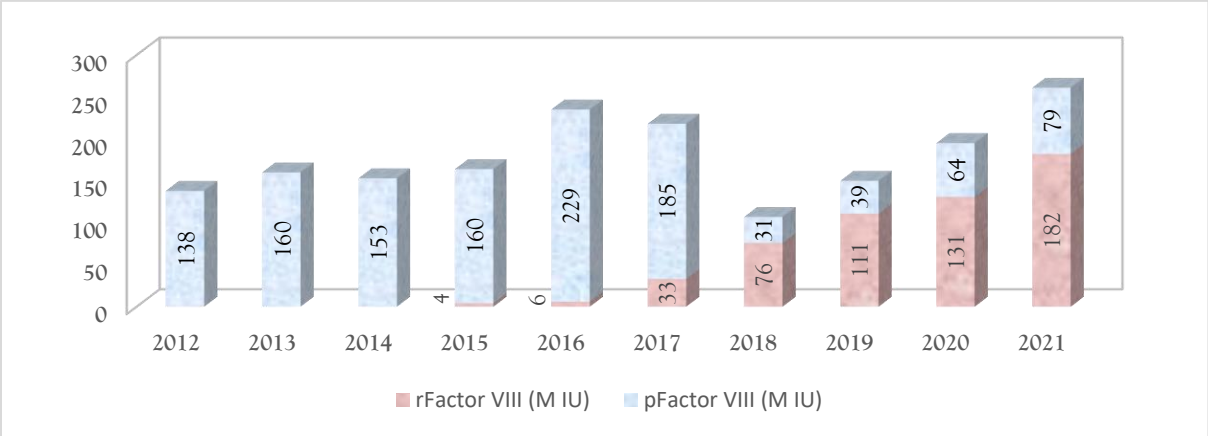


**Figure 3.** 10-year overview of Factor VIII consumption in Iran (M IU)

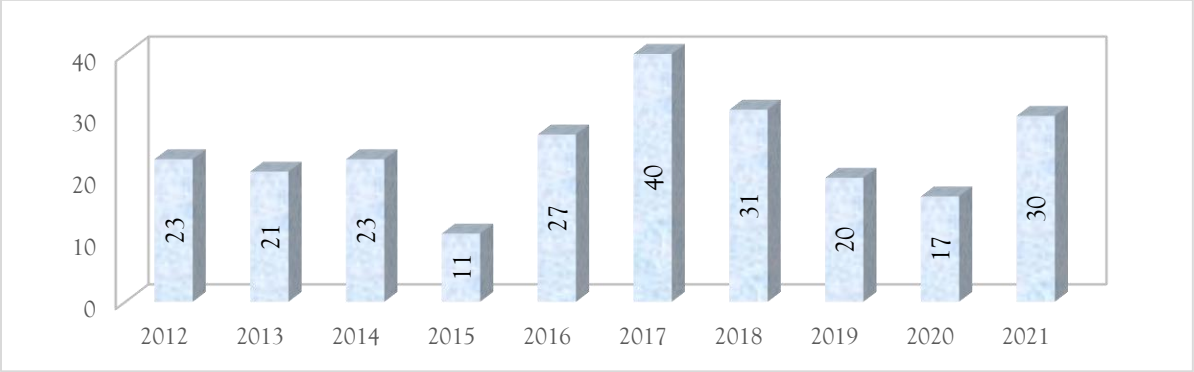


**Figure 4.** 10-year overview of Factor IX consumption in Iran (M IU)



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recommendations for collecting human plasma for supplying local needs.

Collecting sufficient plasma to supply patients' needs has been facing many challenges and referring to the evidence-based clinical needs which are aligned with therapeutic guidelines that may lead to rational PDMP use, and rational planning for plasma collection according to the real need (36).

The supply of PDMPs in Iran is mainly covered by contract fractionation with European fractionators using Iranian plasma. In 2017, a local private company established a plasma fractionator company using the chromatography method with a 50-thousand-liter fractionation capacity, but it put its focus only on producing Albumin and IVIG. In 2022, it is extracted from the published statistics by IRFDA that this company could supply IVIG (2.5 gram) around 154 kg and Albumin around 473 kg. It is expected this company cover more local demands in a not far-fetched future with its capacity expansion to 150 thousand-liter afterward. In 2022, another fractionation plant using the Cohn method went under construction by a private company with around 1-million-liter fractionation capacity per annum. This plant opens hope for covering around 3,775,000 vials of Albumin 20%, IVIG 5 gr, Factor VIII 500 IU, and Factor IX 500 IU per year. Furthermore, Iran possesses elitist academic people who increase the chance to have access to updated technologies for manufacturing PDMPs in coming years.

Implementation of local production of plasma and PDMPs has some significant impacts on economic, social, and health factors including promoting the health of society, increasing technological capabilities, ensuring the availability and affordability of these products, and providing employment opportunities for local workers. Iran is going to expand its plasma industry by increasing the number and capacity of private plasmapheresis centers as well as improving fractionation plants. In this way, the voluntary donation of blood and plasma with altruistic intention, guaranteeing safety, and improving the quality of Iranian plasma and plasma products at the highest level are the main goals and values of Iranian plasma policymakers and stakeholders.

Finally, some decisive factors affect plasma supply and PDMPs manufacturing in Iran which should be highly noticed by policymakers; national plasma policy, private sector investments in the plasma industry (from downstream to upstream), governmental support to increase the capability of plasma donation, futuristic planning for plasma exportation, and international partnerships with national blood service around the world. Although the growing trend in reaching self-sufficiency; 93% for immunoglobulins, and 90% for Albumin, is a great achievement for the plasma industry in Iran, the future road map will not be the same, and this industry needs to pass the country's borders and play its role in the international market.

## 6. LIMITATIONS

One of the main limitations of our study is that the medicines imported are not individually marked by IRFDA, making it impossible to track and monitor the exact amount consumed. We obtained the consumption data for PDMPs from the published pharmaceutical statistics by IRFDA. Additionally, it's worth mentioning that some parts of supplied pharmaceutical products are not registered and are imported in shortage conditions, making it impractical to trace. We hope that with further development of the IRFDA structure, we will be able to accurately track and trace pharmaceutical products to obtain precise consumption data for PDMPs.

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## Conflict of interest

Two of the authors of this publication support from Darman Ara Co. (P.J.S) and also serve as its employees.

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