CRED
Centre de recherche
en économie
et droit

CRED WORKING PAPER n^o 2024-01

Implementing strategic plasma resource self-sufficiency through unpaid plasma donations on the global plasma market

February, 2024

JEAN MERCIER YTHIER*

*Université Paris-Panthéon-Assas, CRED, France.

Implementing strategic plasma resource self-sufficiency through unpaid plasma donations on the global plasma market

Jean Mercier Ythier[1]
Université Paris-Panthéon-Assas
CRED
12, place du Panthéon
75005 Paris
February 2023

The last two decades have seen a considerable increase in the pharmaceutical industry's demand for plasma on a global scale for the production of plasma-derived medicinal products (PDMPs) [1]. In 2019, the year before the COVID-19 pandemic, the consumption of plasma by the fractionation industry reached 69 million liters (ML) [2]. The global market for PDMPs is presently returning to its pre-pandemic base trend of over 7% annual growth [2]. The continuation of this trend over the next few years would mean an increase in demand for fractionation plasma, reaching 93.2 ML in 2026 for the supply of immunoglobulins alone (the main driver of market growth) [3].

Nearly 90% of the fractionation plasma consumed by the industry in 2019 came from paid plasmapheresis performed in dedicated collection centers. The majority of this (approximately two-thirds of global consumption) was collected at FDA-licensed collection centers in the United States [2]. In contrast, the plasma recovered from unpaid whole blood donations accounted for only 8 ML, or 11.5%, of the total collection for fractionation. As a result, the share of recovered plasma in the global supply of fractionation plasma has been cut by two-thirds over the past two decades. From a level of about 30% in the early 2000s, it declined to about 25% in the early 2010s and 15% by the mid-2010s, until the current level (pre- and post-pandemic) was slightly above 10% [2,4].

The above facts imply that it is impossible to meet the demand for fractionation plasma from unpaid voluntary donations *on a global scale* at the present state of manufacturing and biomedical techniques. A simple calculation will illustrate this impossibility. The total number of unpaid voluntary whole blood donations, including family and replacement donations, reported by the World Health Organization (WHO) was 95 million in 2018 [5]. For illustrative purposes, let us assume that these donations are converted to plasmapheresis. Let us further make the optimistic assumption that the average volume of plasma collected per donation is 800 ml (i.e., the maximum volume that can be collected per plasmapheresis in the US). The total volume of plasma collected in this manner would reach only 76 ML, far below the 93 ML needed to meet the projected demand for immunoglobulins in 2026.

Of course, this does not mean unpaid plasma donation must necessarily remain marginal in the provision of fractionation plasma and PDMPs. On the contrary, we will argue that, properly defined, self-sufficiency in strategic plasma resources can be achieved through unpaid plasma donations to appropriately designed *national* blood donation organizations. We will proceed in three short steps: (i) by first recalling why and in what sense plasma and PDMPs should be considered strategic commodities; (ii) by secondly explaining why self-sufficiency in strategic plasma products matters and in what practical sense it can be achieved; and (iii) by

[1] Corresponding author: jean.mercier-ythier@u-paris2.fr

outlining the main characteristics that a national blood organization must meet to achieve self-sufficiency through unpaid voluntary donations.

1-Donated plasma as a strategic resource

Donated plasma has two main uses in the health care system. First, it is used in transfusion medicine as a labile blood product. In addition, it is used by the pharmaceutical industry as fractionation plasma, that is, as the basic raw material for the production of PDMPs.

Donated plasma meets the definition of a strategic resource as "an economically important raw material that is subject to a high risk of supply interruption" [6]. This is the case with plasma-labile products in low- and middle-income countries that do not yet have well-established blood organizations. This is also the case for fractionated plasma worldwide, as demand is growing rapidly and persistently. Episodes of shortages and subsequent rationing in the provision of essential PDMPs, such as intravenous immunoglobulins, have occurred in several countries since 2017, both before the pandemic and under pandemic conditions. This was the case in the United Kingdom (2017–18), France (2018–21), Germany (2021), and the US (2019–21), among others [3]. The COVID-19 pandemic provides a perfect example of the type of event associated with the concept of a strategic resource (i.e., supply interruption). The pandemic resulted in a sudden 14.5% drop in global fractionation plasma in 2020, compared to 2019, a decrease of 10 ML. This global supply shock explains why Germany and the US, which typically collect more fractionation plasma than they need for their own PDMP consumption due to their extensive reliance on paid plasmapheresis, nevertheless experienced the abovementioned shortages in 2021.

These risks are discussed in detail in [1] and [6]. Therefore, we will not recapitulate the conclusions here but instead highlight the type of risk that seems most relevant in this context, namely, the risk of the resurgence of barriers to international trade.

Over the last two decades, the international plasma market has been strikingly consistent with the balance of power in the global economy. It was and continues to be dominated by US exports of fractionation plasma to the rest of the world. In 2019, the US accounted for about two-thirds of the world's fractionation plasma collection and nearly one-half of the world's immunoglobulin consumption [2]. China replaced Germany as the second-largest market for plasma proteins in the early 2010s [4]. In 2019, China accounted for close to three-quarters of the Asia-Pacific region's supply of fractionation plasma, with the latter region itself accounting for nearly one-fifth of both global collection and use of this raw material [2]. The European Union is the third major component of the global plasma market, comparable in size to Asia and the Pacific but far behind the US. It differs from the first two in having a large negative imbalance between the fractionation plasma supply and consumption in the region. For example, the EU consumes about a quarter of all immunoglobulins but collects only 15% of the world's fractionation plasma [2]. This imbalance results primarily in large imports of fractionation plasma from the US [1,2].

The strong integration of the plasma market into the world economy makes it particularly vulnerable to the consequences and dangers of the emerging protectionism that accompanies the profound transformations of international relations now underway. The EU appears to be particularly exposed in this regard because it relies so heavily on imports of fractionation plasma.

2-Self-sufficiency with strategic plasma products

Fractionation plasma and, by extension, PDMPs are considered strategic products for a number of reasons. In particular, these include (i) the classification of PDMPs as essential medicines by

the WHO, (ii) the human origin of these products, and (iii) the risks of supply interruption described above. In addition, these elements of classification have public policy consequences. One of the most important implications is the promotion and implementation of self-sufficiency objectives at the level of the national blood organizations that have chosen to ban paid plasma donations [7].

A basic stake in designing enforceable public policies in this area is defining appropriate self-sufficiency objectives. Here, we suggest that these goals should be based on medical consensus and evidence-based prescriptions of PDMPs at the level of the relevant national blood organization.

A striking feature of the global market for PDMPs is the regional diversity of consumption (and hence prescribing) practices. Let us illustrate this fact with a few examples from the three regions that have emerged as major components of the global market in its present state. A distinctive feature of the Chinese market is the strong demand for albumin due to a mixture of cultural characteristics, local commercial practices, and availability [4]. Regarding immunoglobulins, the consumption shares indicated in Section 1 show large variations in use between the US, the EU, and the Asia-Pacific regions. These three regions account for about one-half, one-quarter, and one-fifth of total consumption, with populations of about 335 million, 445 million, and over 4 billion, respectively. The primary determinant of these data's large disparities in consumption per million people is clearly availability. Finally, if we consider the EU, the consumption of polyvalent immunoglobulins (IgGs) in 2017 was 162.3 in France, 109.3 in Germany, 91 in Italy, and 116.5 in Spain, expressed in grams per thousand people [8].[2] The large difference between France and Italy may be partly due to availability. Nevertheless, other considerations may also play a role, including variations in how IgG prescriptions are managed by the national health systems of the two countries.

Interestingly, the consumptions of Germany, Italy, and Spain are very close, while Germany is a net exporter and Italy and Spain are net importers of fractionation plasma [8]. Availability does not significantly limit IgG prescriptions in Germany, which extensively uses paid plasmapheresis and adequately funds its national health system. These facts suggest that the comparable rates of IgG prescriptions in these three countries may reflect a *de facto* medical consensus, which, if confirmed, could be used to create an explicit medical consensus at the EU level.

Brand et al. showed that the observed increase in demand for PDMPs is not based on clinical evidence [9]. Instead, based on established clinical evidence, they argue that normalization of indications is a necessary prerequisite for sustainable self-sufficiency if plasma donation is not compensated. They also remind us that evidence-based restrictions on clinical indications for labile blood products have been successfully applied over the past several decades, resulting in a nearly 40% decline in their use. Finally, we complement their argument here with a simple comment on the decision criteria of public health authorities. The latter will not put in place costly self-sufficiency policies unless they are based on solid clinical evidence that PDMPs work and are safe.

We want to complement this first basic requirement for defining implementable self-sufficiency objectives with a second, namely, the practical need for flexibility. Under realistic conditions, this generally does not mean full coverage of basic needs in PDMPs. Here are two reasons for the need for a pragmatic interpretation of the self-sufficiency standard by public health authorities. One stems from the fact that definitive quantitative objectives cannot be inferred from the medical consensus recommended above; they can only be derived from the varying conditions of (compliant) clinical practice. A second important reason applies specifically to unpaid plasma donations. The latter cannot adjust in time to variations in

[2] These figures are derived from the data presented in slide 17 of [8].

demand, especially rapidly increasing demand, even if the demand is based on adequate medical consensus.

The Italian experience provides an interesting example of our pragmatic self-sufficiency objectives [10]. The self-sufficiency rates reported for 2017 range from 70% for albumin to 96% for PCCs3, with a rate of 73% for immunoglobulins. Therefore, we suggest that the self-sufficiency objectives of public health authorities be set in terms of large minimum coverage rates at an interval of, say, 75 to 85% of evidence-based need. Public policy implementing these objectives can draw on the open markets of PDMPs but limit their use to covering a marginal, typically variable, portion of less than one-quarter (say) of evidence-based need.

3-Implementation of self-sufficiency objectives for PDMPs from unpaid plasma donations

Under current technological and economic conditions, a self-sufficiency policy is futile for countries that have well-established blood donation organizations that allow paid plasmapheresis. These countries, such as the US and Germany, accumulate quantities of domestic fractionation plasma that are large enough, under current normal conditions, to satisfy their domestic demand and feed significant exports of this raw material. Therefore, a self-sufficiency policy by public health authorities makes practical sense only in those countries that either do not have a suitable blood donation organization or have such an organization but prohibit paid plasmapheresis. We focus here on the latter case. The self-sufficiency policy of such countries will mainly collect domestic fractionation plasma from unpaid plasma donations and achieve domestic production of PDMPs from these domestic resources in raw materials to meet the quantitative self-sufficiency objectives outlined in Section 2 above. This section presents the main structural characteristics we believe the national blood donation organization must meet to implement such a policy. We also briefly assess the plausibility of success in the various dimensions of action.

The relevant structural characteristics are twofold: those related to the organization of domestic plasma collection and those associated with the domestic manufacturing of PDMPs from domestic plasma resources. We will briefly examine them below.

Regarding collection, we have noted that plasma volumes collected from whole blood donations are insufficient to meet fractionation needs. Moreover, they have slowly declined in recent decades, largely due to the slow decline in red blood cells transfusion (which drive whole blood donation). Fractionation of plasma must be done primarily by dedicated plasmapheresis for at least two reasons: (i) the large volumes required and (ii) the divergent trends in transfusion (which is declining in established blood organizations) and in demand for PDMPs (which is growing rapidly in the same organizations). In this case, because plasmapheresis is uncompensated, collection must be done by a nonprofit organization of the public or associative type. A crucial factor in the cost-effectiveness of dedicated plasmapheresis devices is equipment utilization, which is measured in particular by the number of donations per device per day [1]. The collection cost ranges from more than $250/€ per liter in low-intensity conditions, which corresponds to an average of one donation per machine per day, to roughly half of this amount in high-intensity conditions, which corresponds to an average of more than six donations per machine per day. The economic sustainability of the nonprofit's collection requires that the collected plasma transfer price cover the collection cost.

The Australian experience and recent experiments conducted in the Netherlands and France show that a suitable organization allows for a large quantitative expansion of unpaid plasmapheresis compatible with achieving appropriate self-sufficiency objectives [3,11,12]. Practice conditions also suggest that it is difficult, if not impossible, for nonprofit organizations to achieve the cost-effectiveness of for-profit plasmapheresis centers in the fractionation industry. This arises from a fundamental difference in the behavioral patterns of paid and unpaid

donors, expressed primarily in donation frequency, that is, the average number of donations per donor per year [11]. Donor availability is lower for unpaid donations, making it more difficult to achieve the high utilization rates of collection rooms, equipment, and staff (and thus the high-cost efficiency) achieved by for-profit collection centers.

As for the industrial production of PDMPs from the domestic collection of unpaid plasma donations, the second relevant organizational pattern is contract fractionation [1]. The latter consists of contracts negotiated between public health authorities, the nonprofit organization, and a domestic fractionator to produce PDMPs that meet public policy self-sufficiency goals. The legal status of the fractionator is irrelevant in this context. It may be a public company (e.g., the LFB in France), a private nonprofit company (e.g., Sanquin in the Netherlands), or a private for-profit company (e.g., CSL-Behring in Australia, Kedrion in Italy, or Grifols in Spain), depending on the institutional circumstances of the national organization in question. Economic sustainability requires that the industrial operator, whether public, private, not-for-profit, or for-profit, earn a return on capital employed comparable to the returns earned by its competitors in the field. A distinctive feature of the fractionation industry is the share of raw materials (i.e., fractionation plasma) in its total production costs, which is far higher than the average for the pharmaceutical industries [1]. Consequently, economically sustainable contract fractionation requires that the purchase price paid by the fractionator to the nonprofit collection operator for the fractionation plasma be equal to the market price of that raw material. This might require a public subsidy to cover the difference (if any) between the market price and the costs of the domestic collection organization.

In summary, properly formulated self-sufficiency can be achieved through unpaid plasmapheresis. Economic sustainability implies that the sale price of the fractionation plasma from the nonprofit collection organization covers the collection costs of the appropriately dedicated plasmapheresis centers. If these collection costs are higher than the market price of fractionation plasma, a public subsidy from the government budget to the collection organization should make up the difference to ensure the economic viability of both nonprofit collection and industrial production. The cost of such a consistent and economically sustainable self-sufficiency policy to the government budget would then consist of two parts: the cost of the subsidy to the nonprofit collection organization and the cost of the open market purchases of PDMPs needed to cover the gap (if any) between domestic production programmed by contract fractionation and domestic (evidence-based) demand for PDMPs.

Disclosure of interest

The author declares that he has no competing interests.

Acknowledgments

I warmly thank Olivier Garraud and Emmanuel Picavet for their helpful comments and encouragement. I also benefitted from helpful references and encouragement from Richard Forde and Pierre Tiberghien.

References

[1] Mercier Ythier J. The contested market of plasma. Transfus Clin Biol 2020;27:52–57.
[2] Hotchko M. Current market landscape for plasma and immunoglobulins. Proceedings of the IFPA/EBA Symposium on Plasma Collection and Supply, March 15th-16th, 2022. https://ipfa.nl/events/ipfa-eba-symposium-on-plasma-collection-and-supply/

[3] Strengers PF. Plasma Collection and Fractionation in Europe, past, present and future. Proceedings of the IFPA/EBA Symposium on Plasma Collection and Supply, March 15th-16th, 2022. https://ipfa.nl/events/ipfa-eba-symposium-on-plasma-collection-and-supply/
[4] Hotchko M, Roberts P. Recent market status and trends of fractionated plasma products. Ann Blood 2018;3:19.
[5] World Health Organization. Global status report on blood safety and availability, 2021. https://www.who.int/publications/i/item/9789240051683
[6] Strengers PF, Klein HG. Plasma is a strategic resource. Transfusion 2016;56:3133–7.
[7] Tiberghien P. Increasing unpaid plasma collection by blood establishments to ensure availability of plasma–derived medicinal products and blood components in Europe. Transfus Clin Biol 2021;28:331-3.
[8] Strengers PF. Is the yearly collection of recovered/apheresis plasma adequate to ensure European self-sufficiency of essential plasma-derived medicinal products? Proceedings of the EDQM International Symposium on Plasma Supply Management, January 29th-30th, 2019. EDQM, 2021. https://www.edqm.eu/en/news/international-symposium-plasma-supply-management-proceedings-now-available
[9] Brand A, De Angelis V, Vuk T, Garraud O, Lozano M, Politis D. European Mediterranean Initiative for Transfusion Medicine. Review of indications for immunoglobulin (IG) use: Narrowing the gap between supply and demand. Transfus Clin Biol 2021;28:96–122.
[10] Liumbruno G. Regulation of plasma self-sufficiency program: National regulations versus regional regulations and current developments. Proceedings of the EDQM International Symposium on Plasma Supply Management, January 29th-30th, 2019. EDQM, 2021. https://www.edqm.eu/en/news/international-symposium-plasma-supply-management-proceedings-now-available
[11] Thijssen-Timmer D. Obstacles to strategic independence of plasma for fractionation in Europe and the way forward – Is the EU legislation/regulation itself a barrier in any way? Learnings from the Dutch attempt to convert whole blood donors into plasmapheresis donors. Proceedings of the EDQM International Symposium on Plasma Supply Management, January 29th-30th, 2019. EDQM, 2021. https://www.edqm.eu/en/news/international-symposium-plasma-supply-management-proceedings-now-available
[12] Bigey F. Obstacles to strategic independence of plasma for fractionation in Europe and the way forward – Is the EU legislation/regulation itself a barrier in any way? Learnings from the French attempt to convert whole blood donors into plasmapheresis donors. Proceedings of the EDQM International Symposium on Plasma Supply Management, January 29th-30th, 2019. EDQM, 2021. https://www.edqm.eu/en/news/international-symposium-plasma-supply-management-proceedings-now-available