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Review

“Go no Go” in plasma fractionation in the world’s emerging economies: Still a question asked 70 years after the COHN process was developed!

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ABSTRACT

In the late 1980s, following the human immunodeficiency virus (HIV) epidemic and transfusion-transmitted infections from plasma-derived coagulation factor concentrates to hemophiliacs, many “advanced thinkers” claimed that plasma-derived products would be completely replaced by the year 2000 by safe recombinant products in most developed countries. However, things have not turned out that way, due to both the continual progress witnessed in plasma fractionation and viral-reduction technologies and technical difficulties still being encountered in developing more cost-effective non-immunogenic, fully active recombinant therapeutic proteins.

Accordingly, plasma fractionation remains a reasonably healthy industry worldwide, with an ever-increasing volume of plasma fractionated each year to meet the demands for safe and effective plasma-derived medicines at the global level. While high-income countries currently have generally good access to a panel of plasma-derived and recombinant products, desperate shortages of fractionated plasma products remain in developing economies, and patients still have to be treated inadequately.

The steady development of the collection of whole blood in developing economies, to gradually cover the recognized needs for red blood cell concentrates, generates an increasing volume of recovered plasma that is currently wasted. Incentives are therefore high for those countries to consider fractionating such plasma as a means of enhancing their supply of products to treat patients, thereby also decreasing the level of dependence on imported products.

Challenges of local plasma fractionation in developing economies are high, in a context where the technological and regulatory sophistication of the plasma fractionation industry is often underestimated, and the blood supply may be exposed to emerging infectious agents. In parallel, plasma product quality requirements and drivers are evolving in developed economies as is the awareness of clinicians to newer uses of products such as intravenous immunoglobulins, somewhat deviating from what currently remain the basic needs of developing countries in terms of affordable safe plasma products.

Global market trends for plasma-derived products, through plasma fractionation, are still increasing, despite increasing use of recombinant products, and attention is being focused on the five Ws of the fractionation field: which products; where; when; what and how much; and who will be the main suppliers?

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1. Introduction: the need for plasma-derived products is still there and growing

Several plasma proteins (factor VIII, factor IX, activated factor VII, antithrombin, and C1-inhibitor) produced by recombinant DNA technologies using mammalian cell expression or transgenic animals [1] are now on the market. Several decades after their introduction, controversies are still ongoing to determine the benefits, limits, and immunological risks of recombinant coagulation factors compared to their plasma counterparts [2].

One point of agreement is the high costs of these products which have not significantly decreased much since their introduction to the market despite early promises and hopes. Recent technological advances show the feasibility of developing potentially safe modified recombinant products that exhibit improved functional characteristics including prolonged half-lives [3]. In spite of these important developments, there is a continuously increasing demand at the global level for fractionated plasma products, including immunoglobulin G (IgG), albumin, coagulation factors, anti-proteases, and fibrin sealants. The development of plasma fractionation technologies has now expanded the range of plasma products to over 20 [4].

Supplies of plasma-derived products at the national level can be achieved by importation of products, fractionation of local plasma, or contract fractionation. In terms of global demands, the volume of plasma fractionated has been steadily increasing in the last few years, and has now reached close to 35 million liters worldwide, compared to approximately 25 million liters some 10 years ago [5].

Most of the plasma is fractionated in advanced economies where professional fractionators and mature, well-balanced regulatory systems exist to ensure product quality and safety through rigorous licensing and post-marketing surveillance. Approximately 80% of the plasma used for fractionation is obtained by apheresis procedures, most often collected from paid donors in the US and Europe, and the rest (approximately 8 million liters) is prepared from whole blood collected from volunteer, non-remunerated donors, in national blood collection systems that mostly target an appropriate supply of red blood cell concentrates [5]. Most fractionated products are consumed in industrialized countries [6], where the plasma fractionation industry is consolidating to adjust to market forces [5]. The developing world uses a small portion of the fractionated plasma products as a result of product shortages and/or a lack

of purchasing power for these sophisticated medicinal products.

2. Increasing volumes of recovered plasma are wasted: why?

Whereas the number of units of whole blood collected is approximately 30 units/1000 people in high-income countries, in most low- and middle-income countries, this number still ranges 5–10 units/1000 people [7]. As one estimates that the most essential need for red blood cells (to treat malaria-related anemia, fatal hemorrhage, and trauma) requires approximately 15 units/1000 inhabitants, the number of blood collections is expected to increase in those countries, generating additional plasma units. Fig. 1 illustrates what is taking place in many blood establishments of medium-income countries, e.g., in Asia and South America. While in many low-income countries, whole blood is still mostly used for transfusion [8], in medium-income countries, the use of whole blood has decreased, and it is becoming standard practice to perform component therapy to prepare red blood cells, and to some extent platelet concentrates as well. This has gradually generated increasing volumes of recovered plasma.

Part of this plasma is used for direct transfusions to treat clinical situations where its use is justified, but also others where an infusion of albumin, colloids, and fractionated coagulation factors, if they were available and affordable, would represent better standards of clinical practice and patient care. This plasma can be separated into cryoprecipitate to provide a slightly concentrated source of factor VIII, fibrinogen, Von Willebrand factor, and factor XIII. As blood collection increases and the needs for red blood cells surpass that of clinical plasma or cryoprecipitate, this will generate a larger number of plasma units not used for transfusions. In many situations, this plasma is destroyed. It could be used for fractionation if it could meet several conditions that include compliance with quality specifications for fractionation as accepted by a fractionator and approved by national regulatory authorities (NRAs).

The volume of such wasted plasma was estimated at over 5–6 million liters 10 years ago at the global level, and more-recent surveys carried out through the World Health Organization (WHO; unpublished report), taking into account (a) the number of blood donations worldwide (currently estimated to be 103 million annually) [7], and (b) the use of recovered plasma for transfusions and (c)

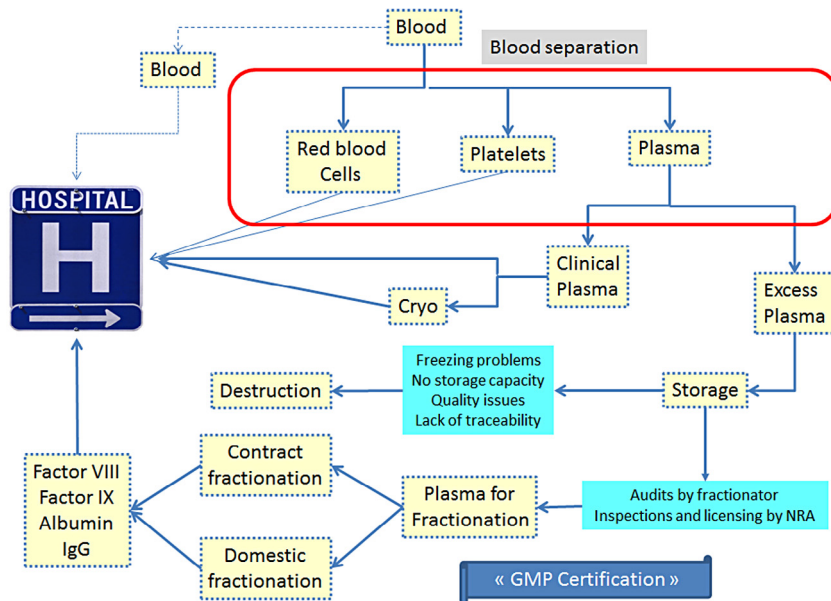


Fig. 1. Wastage of plasma. Illustration of a situation occurring in medium-income countries where blood separation to meet the needs for red blood cell concentrates and blood component therapy generate increasing volumes of recovered plasma. Part of this plasma is used for direct transfusions or for preparing cryoprecipitates. As the blood collection volume increases and the need for red blood cells surpasses that of clinical plasma, this will generate an increasing volume of plasma not used for transfusions. In many situations, this plasma is being destroyed since it currently has no clinical use. It could be used for fractionation and production of fractionated plasma products only if compliant with GMP quality specifications for fractionation, as accepted by a plasma fractionator and approved by national regulatory authorities (NRAs).

for fractionation, suggest that, actually, close to 9.3 million liters of recovered plasma may be currently wasted or discarded yearly. More countries are therefore becoming interested in fractionation programs that make use of such wasted plasma to improve access to plasma-derived products of assured quality. One major issue is that currently collected plasma in low- and medium-income countries typically does not meet specifications for fractionation and is therefore discarded. This situation may however gradually improve since the recent listing of blood components on the WHO Model List of Essential Medicines [9] that should contribute increasing government awareness on the need for well-organized blood services, and implementation of good manufacturing practice (GMP) principles in blood establishments for improved product quality, safety and supply.

3. Complexity of plasma fractionation technology

The production processes of all biological products (recombinant proteins, monoclonal antibodies, vaccines, antivenoms, and plasma products) are, together with the starting material, a very important factor in the quality and safety, explaining the high level of regulatory focus on manufacturing methods and process validation. In plasma fractionation, product specification is linked to the manufacturing process, and product quality depends on both the plasma and the process. It is often not realized that, among all manufacturing industries of biological products, the plasma fractionation downstream technology has reached a high, if not the highest, level of sophistication. This complexity is frequently underestimated.

Plasma fractionation is unique in a way that it requires integrated downstream purification and viral-reduction processes of a level of complexity that is demultiplied by the number and biochemical diversity of protein products – usually more than four or five – made from each plasma batch. Each product-extraction procedure includes several critical purification steps encompassing precipitation, chromatography, depth filtration, ultrafiltration, and sterile filtration that should be carefully validated, controlled, and monitored for implementation at a production scale. Extraction processes should be mild to avoid the risks of alterations that could lead to protein antigenicity or activation, and associated side-effects, like hypotension, fever, and thromboembolic events. In addition, all products should typically go through two dedicated and complementary viral-reduction procedures, either two viral-inactivation steps, or one viral-reduction treatment followed by one viral-removal step.

Experimental studies should be done to show the capacity of the process to remove prions [10]. Fractionation plants should be designed with great care based on the core fractionation processes of all products, and working procedures should be strictly controlled and monitored to avoid risks of cross or downstream contamination. In addition, because human plasma is susceptible, if not continuously exposed, to threats of new, known and unknown, infectious agents, continuous vigilance is needed to safeguard safety. Finally, the level of sophistication and requirements of quality control tests are continually evolving as new clinical information from pharmacological surveillance of products is obtained, as was recently the case

in relation to thromboembolic risks associated with immunoglobulins [11].

4. Contract fractionation: a pragmatic way to go

Because of the technological challenges mentioned above, combined with economic considerations linked to the high capital investment needed for a domestic fractionation facility, a contract plasma fractionation phase is a reasonable approach to consider, at least for an interim period of time of no less than 5 years, before starting domestic production, if and when justified. In such a situation, plasma is sent to a licensed fractionator, and final products are returned to the plasma supplier for use in the country after licensing. Such a program can be implemented within a relatively short time (1–3 years) provided a sufficient plasma volume can meet the fractionator's and regulatory authority's requirements [12]. This involves the signing of a contractual agreement between the plasma supplier and fractionator. Contract fractionation requires strict oversight from regulatory authorities of both the plasma suppliers and fractionators to ensure quality requirements of the plasma for fractionation and fractionated end-products. Invariably, blood establishments, subjected to inspections and audits, will have to improve their working methodologies, practices, and procedures to follow fractionation production criteria for plasma needed by fractionators and regulators [12].

Examples show that contract fractionation can be performed for yearly volumes of plasmas of as low as 10,000 L, although some fractionators would prefer a range of at least 30,000 to 50,000 L considering the regulatory work (e.g., blood plasma collection audits and product licensing) and logistics involved to ensure that the plasma meets quality specifications, and products can be licensed. Existing contract fractionation agreements do not generally involve more than 200,000 L of plasma per year and per fractionator. Typically, products obtained from such contracts include factor VIII, albumin, IgG, prothrombin complex, and/or factor IX.

Although plasma fractionation activities may be expensive, some countries have reported substantial savings associated with implementing fractionation activities of normally discarded recovered plasma, provided a convenient product balance is achieved. Beneficial impacts on the quality and safety of all blood components through the introduction of the concept of GMPs have also been observed [6,13–15].

5. Domestic fractionation: the hard way to go?

Embarking on a domestic plasma fractionation program is challenging in technical, financial, and regulatory terms, as this industry is highly regulated at the global level. Depending on the local market situation and the landscape of government support and commitment, domestic fractionation may be considered if reasonable prospects to generate at least approximately 300,000 L of quality plasma per year are objectively demonstrated [6]. This plasma can first be obtained as by-products of the preparation of cellular components from whole blood. When demand for plasma products increases above the capacity that can be

generated from recovered plasma, additional and dedicated collection of plasma by plasmapheresis should be considered.

Apheresis collection can also be implemented at an early stage to prepare hyperimmune plasma for the production of specific immunoglobulins (hepatitis B, tetanus, rhesus, etc.), as some are essential therapeutic products on the WHO Model list of Essential Medicines. Designing, building, qualifying, and validating a plasma fractionation facility is a very specialized activity that requires sharp expertise in many fields, including biological product manufacturing and engineering. Experience shows that a partnership with an existing plasma fractionator, or a technology supplier with hands-on practical experience in plasma fractionation and proven success in licensing plasma products, appears preferable. The role of the engineering companies should not be underestimated as it is crucial.

A skilled engineering company with an understanding of the manufacturing and regulatory requirements of biologicals is necessary. Both the fractionator and engineering company are required to provide professional training of operators and powerful transmission of know-how to their forthcoming fractionation partner.

It should be kept in mind that although several contract fractionation projects are ongoing, the world is still looking for actual completion of a successful technology transfer agreement between an existing fractionator and a partner in an emerging country. Although this is certainly not the only possible model, a phasing process that allows progressive local production of plasma derivatives is seen as a reasonable way to implement a successful program. Fig. 2 illustrates such a phasing comprising a period where all products are manufactured abroad on a contractual basis (A), followed by preparation of intermediates at the local level and finishing steps abroad (B), preparation of a first finished product (such as albumin) locally while the finishing steps of the other products are still done abroad (C), and finally, complete manufacture of all products at the domestic level with assistance from the technology supplier (D).

This phasing allows the gradual education of operators in production steps like plasma thawing and cryoprecipitation, ethanol fractionation technology, chromatographic purification, viral-inactivation and viral-removal processes, aseptic filling and freeze-drying, and production of production fluids, and their associated quality control and quality assurance requirements. This also allows a phasing in of financial capital requirements.

6. If “go”, then which process?

The experience gathered over the past few decades on the combination of ethanol fractionation with chromatography to produce a large range of plasma derivatives [4] makes this technological approach a serious contender for technology transfers to emerging countries. The technology, including its advantages and limitations, is well known, and resulting products have been used on the market for a long time. Regulatory authorities in developed countries are familiar with it, even if each fractionator has its own know-how and specific combinations of production steps around a similar core fractionation process [4,16].

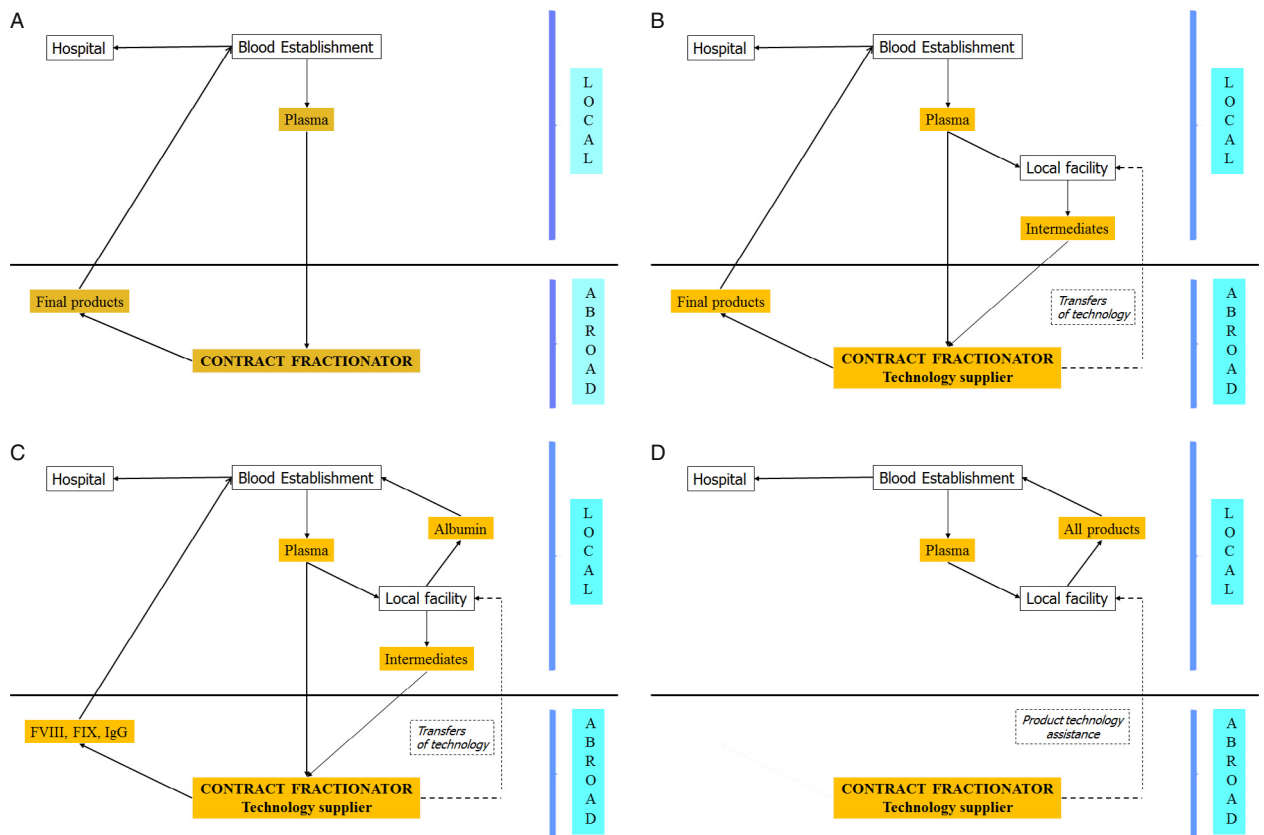


Fig. 2. A phasing from contract fractionation toward domestic fractionation. (A) Time-frame when plasma is sent abroad and plasma products are fractionated on a contractual basis and returned to the plasma supplier; (B) preparation of plasma intermediates (cryoprecipitate, fractions I + II + III, fraction II, and fraction V) at the local level and finishing steps abroad; (C) preparation of the first finished product (such as albumin) locally while the finishing steps of the other products are still carried out abroad; (D) complete manufacture of all products at the domestic level with assistance from the technology supplier.

New technologies, however, are being evaluated in both developed and emerging economies that intend to provide either higher yields for current market drivers, higher flexibility to adjust to countries' needs, or ease of implementation [17]. They include fractionation processes based on multi-sequential purification processes using mimetic ligands [18], mixed mode, high-density, expanding bed adsorbents [19], large-scale preparative electrophoresis technology across membranes of controlled porosity [20], viral inactivation and mini-pool protein fractionation in closed-bag production systems [21,22], and aqueous two-phase systems (ATPS) using a mixture of polymer(s), salt, and water [23]. These novel technologies should be proven to meet current quality, consistency, and safety standards.

7. By the way, how are fractionation technologies coping with new infectious threats?

As many new infectious agents are threatening particularly low- and medium-income economies, one critical question often being addressed is the capacity of current and newer plasma fractionation technologies to cope with the threats that these pathogens are specifically creating in these countries. Emerging viral agents that have impacted

the blood supply in the last few years include, to name a few, West Nile virus (WNV), dengue virus (DENV), chikungunya virus, severe acute respiratory syndrome (SARS) virus, various avian flu viruses, Middle-East respiratory syndrome coronavirus (MERS-CoV), and hepatitis E virus (HEV) [24,25].

There are concerns that viruses belonging to the Filoviridae family, particularly the Ebola virus, may enter the blood supply and affect the quality and safety of industrial plasma products. The traditional tripod of safety of blood and plasma products for well-known blood-borne viruses [human immunodeficiency virus (HIV), hepatitis B virus (HBV), and C virus (HCV)] is, in addition to a well-structured blood collection organization [26], selection of donors, testing of blood donations, and viral-reduction treatments implemented during plasma product manufacture [27]. In early phases of a new infection, selection of donors and testing of donations might not be effective or applicable if infective donors are asymptomatic or a test is unavailable. In such situations, viral safety relies solely on the robustness of viral-reduction steps already in place in the manufacturing process of plasma products. Over the years and following the identification of the transmission of HIV, HBV, and HCV enveloped viruses, and then non-enveloped parvovirus B19

and HAV viruses by plasma products, substantial progress has been made by the plasma fractionation industry, under close supervision of the main regulatory authorities, to develop, validate, and implement effective viral-inactivation treatments. For instance, a technology like solvent-detergent has been able to eliminate risks from lipid-enveloped viruses, including agents like WNV, DENV, SARS, avian influenza virus, and chikungunya when they entered the plasma supply and before the introduction of test procedures, if any, for viral markers [28–30].

It is expected that the robustness evidenced by this technology, and possibly other technologies against enveloped viruses like caprylic acid treatment, can safeguard plasma products from the risk of all lipid-enveloped infectious agents, including filoviruses. To address the risks associated with non-enveloped (in addition to enveloped) viruses, a technology like nanofiltration provides generic and controlled removal of infectious agents based on a size-exclusion mechanism [31], while pasteurization has also demonstrated robustness against a large range of enveloped and non-enveloped viruses [27]. Under the current state of viral-reduction technology implemented by plasma fractionators and multi-step purification procedures responsible for removing viruses, it seems scientifically reasonable to conclude that potential residual infectious risks for most plasma products would be restricted to emerging resistant small (<15–20 nm) non-enveloped viruses.

8. Conclusions

Global needs for plasma products are still unmet. Recombinant coagulation factors, although available in increasing amounts and from more producers, are not expected to cover the needs in developing countries for several years to come. Albumin, for cost reasons, and intravenous immunoglobulins, for technical and scientific reasons due to their biochemical diversity and multiple specificities, cannot easily be produced by recombinant technologies. Many developing countries have an excess of plasma generated as a by-product of the production of red blood cell concentrates.

This plasma could be used as a source of fractionated plasma products. In most situations, the quality of this plasma does not meet the requirements for fractionation. Discarded recovered plasma can be used for fractionation, as a raw material for the production of pooled plasma derivatives, only if quality and safety criteria and procedures used within blood establishments are improved and meet standards needed by fractionators and imposed by regulatory authorities [12]. Strong government support to enhance the quality of blood collection organizations is therefore required. Plasma meeting regulatory requirements for fractionation can be processed through contract agreements into various derivatives. Some countries have found such organizations to be cost-effective and useful to ensure access to products, while a few others are building or considering domestic facilities. Regardless of which technologies are selected, it is important that both plasma collection and fractionation are performed following standards established at a global level to ensure end-product safety and ultimate improvements in healthcare systems.

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