



***Annals of Blood* special issue on plasma fractionation**

It has been a great pleasure and an honor to act as Guest Editor of this special issue of *Annals of Blood* (AOB) devoted to human plasma fractionation. This issue assembles up-to-date and dedicated articles specifically written by world leaders in the field of plasma fractionation.

Plasma fractionation is expected to remain in the years to come, an important technological means to prepare a number of essential life-saving medicines to treat various immunological and bleeding disorders, and other pathologies often associated with congenital or acquired plasma protein deficiencies. The variety of pathologies that can be treated by industrial plasma products, such as immunoglobulin G, various coagulation factors, albumin and others is clearly described by Dr. Paul Strengers in a comprehensive chapter that highlights the need for evidence-based clinical applications of plasma products (1).

The market analysis presented by Matthew Hotchko and Patrick Robert gives an updated view on how the needs for various plasma products, including some specialty products, is expected to continue growing in the years to come (2). It addresses also the expected trends for an increasing volume of plasma for fractionation needed at global level. This chapter leads us, among other points, to question the current fragility of the plasma supply as most is currently collected in a single country (USA) to cover global needs.

In two parts, Dr. Albert Farrugia shares with us his long personal journey and extended expertise in the manufacture of the various generations of factor VIII products from crude non-virally inactivated preparations to the modern double virally inactivated concentrates purified by chromatography (3,4). The benefits of some of these preparations in terms of lower antigenicity is highlighted. Dr. Farrugia provides however a useful reminder on the relatively low efficiency of the plasma fractionation process which over the years has not found efficient or reliable ways to improve factor VIII recovery.

It is often poorly appreciated that plasma fractionation is one of the most complex domains in the biological product/biotech industry. The complexity to establish a national plasma fractionation program is both organizational and technological, and the associated financial costs are most often under-estimated. It is therefore important to look how several emerging or developing countries are tackling the implementation of a domestic plasma fractionation industry. We have selected four representative countries that illustrate different scenarios.

In his chapter, Dr. Ranjeet Ajmani describes the current situation in India, a very large country with multiple blood banks and very limited historical experience in plasma fractionation (5). In a context where the collection of apheresis plasma is not allowed, India is still in lack of a structured blood and plasma collection organization capable to generate enough plasma of homogeneous quality for fractionation. A further difficulty is linked to the fact that about 40% of the collected blood is not separated into components, including plasma. This results in major shortages in plasma products nationwide. Although a fractionation plant has been planned at national level, delays in construction have been encountered.

The challenges associated with the construction of a domestic plasma fractionation facility are uniquely illustrated by Dr. Luiz Amorim (6). Several, small-scale plasma fractionation facilities have been closed several years ago in Brazil due to poor efficiency and lack of GMP. It was decided to build one plasma fractionation facility to process the plasma collected at federal level. In his chapter, Dr Amorim describes the specific difficulties that have been encountered in this attempt in the identification of suitable engineering companies and the recruitment of skilled manpower, among many others of regulatory, commercial and political natures. The lessons learned from the Brazilian experience can be of value for other countries considering to embark into the construction of a domestic facility, by helping them to address, from the start and in a professional and informed manner, the challenges.

In that regards, the experience provided by the plasma fractionation program developed over the years in South Africa is rich of valuable information. Dr. Jen-Han Omarjee et al. describe how the long existing local model of plasma fractionation has been capable to evolve and address local challenges to ensure the access by the local population to a comprehensive range of affordable plasma derivatives (7). A key factor of this achievement is the strategic partnerships established with the South African Blood Transfusion Services as provider of plasma for fractionation meeting the needed quality requirements. Good working relationship with the local regulatory authority is also seen as a main element in the success of the program.

The current situation of plasma fractionation in China is reviewed by Dr. Ya Wang et al. In this chapter, the authors

address the specific issues faced by the Chinese plasma fractionation industry (8). They highlight how strategic the procurement of plasma products is important in this large country of more than 1.3 billion inhabitants. One major current challenge is to further strengthen and modernize the Chinese plasma fractionation industry to ensure “self-sufficiency and strategic independence” in a wider range of plasma products, potentially serving as a model of development for developing countries.

One of the difficulties faced in many countries is the capacity to generate recovered plasma of a quality meeting the specific set of requirements of plasma fractionators and regulators. Producing quality plasma for fractionation is in any blood organizations under the responsibility of a skilled quality assurance manager. Dr Shun-Chung Pai describes in a detailed manner based on his own experience the role that is being played by a quality assurance person in ensuring at all levels of the production chain, that recovered plasma can meet the most stringent and adapted requirements in donors screening, testing, processing, storage, traceability, and documentation required to be eligible for fractionation (9).

It is impossible to address plasma fractionation without highlighting the requirements to ensure an optimal virus safety margin of fractionated products. In his chapter, Dr. Thomas Kreil explains the current virus removal/inactivation safety tripod put in place by the plasma fractionation industry all along the manufacturing process (10). Those measures are essential to ensure the degree of virus safety now reached by plasma products produced in a highly regulated system. Among those, the implementation of dedicated virus inactivation or removal methods during the fractionation process itself is playing the most crucial role and is proven to be an almost absolute safeguard against emerging viruses. Always remembering mistakes from the years 1980–1990’s, which have led to virus transmissions in particular to hemophiliacs, is a safeguard for continuously ensuring the virus safety of the modern plasma products, as well as that of other therapies, including cell therapies and advanced therapy medicinal products involving the use of materials from mammalian/human origins.

The modern plasma fractionation industry is highly regulated in industrialized countries. In their respective chapters Dr. Mark Weinstein (11) and Dr. Françoise Rossi (12) offer a very detailed and updated view of the regulation of plasma fractionation and plasma products in USA and France/European Union. The regulatory framework in place in those countries is essential to ensure the current quality, safety and efficacy of plasma products, including in the US context where most of the plasma collected for fractionation is obtained from paid donors donating by plasmapheresis. The scientific knowledge developed over the years of the plasma fractionation process and the quality and safety criteria of plasma products is tremendous. This has allowed to develop an informed and mature regulatory environment, where regulators and producers can jointly address important quality and safety requirements in a documented and scientifically-based manner.

While plasma fractionation is a relatively old industry established mostly in high-income countries, still the world is facing shortages in all plasma derivatives. The lack of product is most specifically affecting hemophilia patients living in low-medium income countries. Unavailability and unaffordability of industrial virally-inactivated coagulation factor products (particularly factor VIII, factor IX, fibrinogen, von Willebrand factor concentrates) in these countries leads to the clinical use of crude, non virally inactivated blood fractions like cryoprecipitate and plasma as emergency treatment of bleeding disorders. This has led to the development of technical initiatives in Egypt for the implementation of low-cost, in-bag solvent/detergent virus inactivation of cryoprecipitate and plasma. In their chapter Dr. Magdy El-Ekiaby and colleagues present the licensed medical devices developed for implementing this virus inactivation treatment (13). The authors review the extensive scientific data describing the quality and safety of such mini-pool S/D-cryoprecipitate that is now routinely used in Egypt and contributed to stopping the transmission of enveloped viruses, most especially hepatitis C virus, to hemophiliacs, and improved their quality of life by allowing home therapy. Such initiative is supported in two chapters written by Dr Jean-Claude Faber who advocates, in a context where several virus inactivation technologies have been developed for plasma or cryoprecipitate, the need to promote in a global initiative the “local preparation of virus inactivated cryoprecipitate in developing countries” with the collaboration of international partnering organizations (like WHO, ISBT and others) and national stakeholders (e.g., competent authorities, blood suppliers, patient associations) (14). Using a virally-inactivated cryoprecipitate is in Dr. Faber’s opinion, a cost-effective way to fill the virus safety gap existing between untreated cryoprecipitate currently used, and unavailable or unaffordable industrial concentrates (either plasma-derived or recombinant), thereby improving patients’ safety. Dr. Faber also advocates the fact that clinical use of (virally-safe) cryoprecipitate is associated with a lower risk of development of anti-factor VIII inhibitors. Inhibitors development occurs most particularly in previously untreated (or rarely treated) patients exposed under emergency situations to massive doses of factor concentrates, especially when they are

prepared by some recombinant technologies (15).

To complete this series of articles on plasma fractionation, I have written an update on current plasma fractionation technologies that highlights the scientific developments in the field over the years and illustrates how modern plasma products have now reached an unprecedented level of quality and safety (16).

Together with the editorial board of *Annals of Blood*, I am hoping that this thematic issue on plasma fractionation can serve as a valuable educational hub to readers having interest in plasma fractionation today and in the future. I wish to address my most sincere thanks to all the authors who have contributed in a professional manner in preparing this quite unique issue as well as Dr. Yongshui Fu for being the excellent initiator of this special issue.

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