Securing Safe Plasma for Fractionation the Duty of any Country

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Introduction

In an international framework of cyclical plasma products shortage, it is surprising to consider the amount of plasma that is thrown out of the transfusion services due to either a lack of updated quality procedures or an absence of consideration for its potential added value through fractionation. Even though the preparation of Fresh Frozen Plasma (FFP) is warranted in almost all countries - including the less developed - by at least some leading blood collection facilities, the number of countries having actually reached a fractionation grade plasma quality remains too limited in the twenty-first century.

On another hand, what is the profitability of investing in a significant package of transfusion related SOPs, screenings, qualified people, fixed assets for processing, freezing and storing if the plasma is not processed into valuable finished products ? Indeed, the concomitant extreme concentration of the worldwide industry and frenetic race between central regulatory agencies to raise additional barriers to plasma issued from non-member countries are more and more prohibiting the access of non-Western starting material to the largest and most modern facilities. Does it mean that developing countries should not have interest in increasing and reaching the fractionation grade for their domestic plasma resources ?

Is the plasma industry interested in regulatory barriers ?

The progressive and continuous elevation of the standard of care in a growing number of countries is fostering an increased consumption of the most life-saving drugs to which blood products belong. Even though a significant part of the humanity has still limited access to these therapeutics, the last five years have shown that chronic diseases such as haemophilia and primary immuno-deficiency are more and more considered as a priority in the public health system of major countries, for instance the Russian Federation or China.

Accordingly, the industry is tailoring its plasma resources to this natural growth but isn't there a discrepancy between on a one hand the major reservoir of market located in the Southern hemisphere and on another hand the exclusive sourcing of the industry concentrated in Europe and the US ? This contradiction is linked to the economy of scale that the in-

dustry is placing in securing the maximum volume of plasma within the most limited and concentrated origins. Such economy is linked to the growing cost of referencing a new plasma origin at the regulatory level in Western countries where the facilities and most profitable markets are located.

This cost is itself driven by the now well established Risk Management Plan (RMP), new paradigm of the regulatory evaluation of risky business such as blood and biological products.

For a given plasma origin, the RMP shall identify the epidemiology of model viruses within the country as a whole, then the donor population, the first or repeated donors and finally the screening procedures applied to such populations. Anyone can easily understand that the difficulty to safely pass through this RMP is tightly linked to the sanitary management of viral infections in a given population or in a shorter way, to the Gross Domestic Product (GDP) of a country. Historically, this kind of principle has rebuked all US manufacturers from engaging in any contract manufacturing agreement with any country in order to prevent exposing their US tanks and pipes to the mix of different plasma origins. The potential endorsement of the same approach by European regulators could lead the industry to question whether entering into contract manufacturing can harm their position in the EU core market in front of the tentative change it can induce in their RMP assessment.

Even though there is not yet any enforceable drastic regulation prohibiting non European plasma origins in European plants, there is a growing control on imported plasma and all stakeholders have to be aware of the consequences that such a ban can represent to the emerging world, a full dependence on foreign industry and plasma resources. In reaction, nobody can be surprised about the local reaction against such situation which can result in limiting the access to standard of care for budget constrains reasons or inducing indulgence towards lower quality solutions.

Self-sufficiency, a moving concept

In this fluctuating framework, what could be the position of developing countries in order to warrant their population with a good standard of care in blood products while decreasing their risks of dependence on cyclical price or volume pressure from a foreign industry ?

In the nineties, some experiences of contract manufacturing for small developed (Luxembourg) or developing countries (Tunisia) have paved the way for a tentative valuation of local plasma resources in the spirit of self-sufficiency. Focusing more on emerging nations, it was also for them an opportunity to increase the global quality and safety level of the national transfusion organisation and make available blood products that were barely available before, even though the specifications of the plasma and

the finished products could be perceived as less stringent than in the Western countries. At that time, implementing the basic requirements for fractionation grade plasma was already representing a significant investment (computer assisted treatment of logistics and traceability, temperature monitoring and prevention of disruptions, upgrade of laboratory SOPs, etc ...). When adding the industrial partner's own range of screening including nuclear acid testing (NAT), the contract manufacturing operations were a significant jump in the global safety management of the blood and plasma resources while the political valuation of domestic resources was a first reward for the authorities in charge of transfusion and healthcare procurement. Nevertheless, implementing such local improvements is far from being cheap and even though one of the drivers of self-sufficiency could be presented as an economy on plasma costs, the first products coming in are more expensive than commonly imported industrial drugs for obvious economy of scale reasons.

This is the bridge with the second impediment to the contract manufacturing, the critical mass. Describing a plasma origin (that we'll summarize as a Plasma Master File, PMF) is a huge bench of administrative work for contract manufacturing.

Constituting, filing, maintaining a PMF is a hard duty for a Western manufacturer and the persistent quicker scale up of the regulatory RMP requirements compared to the only progressive improvement of the local quality level is generating a permanent updating workload that does appear in the bill.

For the most advanced countries, it resulted in the discontinuation of the contract manufacturing to switch to the simple direct sale of their plasma to operators. This short cut is also a way to generate cash while preventing any criticism against the concomitance of trading activities for both plasma and finished products under the same legal entity. But for the developing countries, we are reaching a point where any contract manufacturing contract requires a critical volume of plasma to be warranted for at least three to five years before entering into a huge initial investment which amortization takes longer and harder for both stakeholders, including the industrial. Nevertheless, experiences have been pursued in some cases with a reasonable success, quoting some countries in the Far East dealing with Australia and on the other side Brazil dealing with France.

We have therefore acknowledged above that investing in fractionation grade plasma for a developing country is leading to secure blood products under self-sufficiency in a more expensive way than importing the whole of such products, at least for a couple of years. As far as the manufacturer is concerned (at least under the Western regulations), qualifying a contract manufacturing customer

is significantly more expensive in registration, sanitization, dedicated columns and material, etc ... than seeking to enlarge its existing standard Plasma Master File procurement, inducing a higher transfer price for the products or service to the self-sufficiency candidate than for the routine commercial production.

Where is therefore the interest for an industrial player to cope with this contract manufacturing challenge ? There are two answers to this question. The “beautiful” one where the commercial company is locally supported by the public organism in charge of self-sufficiency in order to get faster registrations, access to the prescribing community and some other stakeholders (purchasers, regulators, patients, etc ...), compensating for the lower profitability of the contract manufacturing activities. The “weird” one where a commercial company is bargaining for the service but subsequently creates obstacles to the actual implementation of the self-sufficiency program, delaying qualification, arguing higher costs and investments, etc ... in order to protect the existing importation system to the best interest of the global industry. Examples of both reasons can be found in the past fifteen years in different countries reasonably widespread on the earth and is perfectly applicable to industrial facility technology transfers as well.

Although the picture could appear somehow discouraging for countries who are thinking about valuing fractionation grade plasma production and investment, some established benefits and future trends could support such decision. On the benefit side, a better plasma induces the global improvement of the general safety of red cells, platelets and cryoprecipitate: tracking through a computer assisted program and testing mini-pool to reach individual NAT for most serious viruses is saving lives, both at the donor and recipient levels. It is also improving the confidence of the population in the transfusion system and promotes the value of donating.

Economically, the streamlining of the blood separation, qualification and component ultra-low temperature storage in a limited number of regional production centres is driving part of the costs down and makes the transfusion system more eligible to an agreement by the Western regulatory agencies, key to the valuation of the plasma for contract manufacturing (for instance through a more limited number of audit by the foreign authorities and the production of reliable regional epidemiological data).

There is also an opportunity to consolidate the blood and plasma donor population by performing targeted promotional campaign towards donation: contribution to the travel expenses, to regular healthcare check-up, federation of groups with corporate acknowledgement for best regular donors, etc ... Such ethical promotion is allowing to stabilize the

population, to make availability planification for cellular products and to advocate more efficiently for targeted plasmapheresis and plateletpheresis.
But if this already significant investment is not sufficient to share a national PMF with Western countries, should applicants give up on such challenge ?

The courage to shift towards self-sufficiency for the sake of public health

A new emerging concept of these last years could be considered as a new potential answer to this question. In front of the above regulatory gap between continents and the consolidation of the industry, a growing number of countries is seeking to own their national fractionation facility. Brazil has already initiated such project. Further reflexions are ongoing in numbers of countries which have access to a critical number of blood and plasma donations, pre-requisite before any financial consideration.
Two key success factors are to be addressed upfront by the decision makers : access to plasma raw material and standard of care for the use of finished products. The latter is of course closely linked to the global population as well as to the blood donation culture of a given society. If there are barriers to frequent or regular donation among the bulk of the population, the leverage has to be found in the ability for the local investors and healthcare providers to open and run new plasma collection facilities. The sanitary and political regulations should be adapted to ease the emergence of such a segment of plasma supply. Considering the huge fixed and working capital that a new fractionation facility requires to build, validate and operate, its occupied annual throughput capacity is the key leverage for the ordering party to get a return at any time and convince financial stakeholders to step in. Accordingly, finding regional fractionation grade plasma beyond the national resources will become a driving force for these industrial projects. Even though geopolitics and healthcare harmonisation is not the easiest couple to accommodate, the opportunity for a country without a critical population (or plasma resources or financial capability) to benefit from a neighbouring new industrial facility should induce political reflexion to allow plasma to circulate more easily for contract manufacturing.
For the use of finished products, there is almost no investment needed to increase awareness about the added medical value of factor VIII and albumin to the specialists in charge. Further availability of coagulation factors could even induce new behaviour in targeted populations such as prophylaxis for younger patients.
The situation is less obvious for immunoglobulins (IVIG) as primary deficiency could be under-diagnosed and auto-immune diseases treated with cheaper but less satisfactory alternatives (corticosteroids or others).

Accordingly, the implementation of a self-sufficiency program should be preceded by an effort in training the relevant physicians (paediatricians, neurologists, internal medicine specialists, etc ...) about the proper use of IVIG and the implementation of larger programs of education on diagnosing and treating rare diseases. The limiting factor to this bright perspective for developing countries to upgrade and value their plasma for fractionation in new regional facilities is the access to technology. There is a tentative contradiction between the growth pursued by the industry in the famous ongoing consolidation process and the potential competition coming from regional projects dealing with self-sufficiency and fuelled by locally qualified plasma. This is probably why no project started wherever until now and benefiting from the technology of a well established Western player has ever released a finished product on the market. The concentration of the industry is the toughest threat to technology transfer. Of course, there is no new scoop in such acknowledgement regarding those who never in the past signed any contract manufacturing agreement (mainly companies owning facilities located in the US).

But what about the remaining "small European players" and how should they consider this emerging trend ? With the increasing size gap challenge they face, particularly in the most competitive emerging markets that are by the way also the tomorrow reservoir of growth, one can imagine a new strategic reflexion. Imagine that this new activity could be an opportunity to spread their product technology franchise through delocalised new sites, it would be a way to gain market share without compromising any core activity that is based on different regulatory patterns under the Western rules. Even though nobody has access to the strategic planning of the industry, it is doubtless that the price to get access to a new market in the following years will be a growing problem for the outsiders. New business model for market access should therefore be considered as time goes by. If the reflexion is taking too long, no one should be surprised to see yet unidentified emerging industrials stepping in the challenge and establishing a new global economy of the business.

Regardless of who will be the industrial pioneer, it is probably a good period for the applicant nations to self-sufficiency to make two parallel strategic reviews. For those countries benefiting from the above quoted key success factors for building a profitable regional fractionation facility, assess and reassess their national, regional plasma resources and tentatively generate regulatory contacts with selected countries to prepare some common ground to plasma specifications. As a return for countries which have infra-critical parameters, it will be highly visionary to invest in blood collection organisa-

tions and generate plasma volume, including quality and logistics upgrade in order to be ready on time for contract manufacturing with their new operating industrial neighbours. If the process is safely conducted and whenever for any economic or medical reason, given organisations are not able to profitably value the three minimum key products out of the fractionation of their domestic plasma volumes (IVIG, factor VIII and albumin), there will be still an opportunity for them to sell the plasma to the third parties running the regional facility with alternative underserved target markets, bringing a return on the investment for both parties.

Conclusion :

The future years could see a divergence between industry economy and nations' healthcare needs. There is a rationale for a high investment sector such as plasma products to consider growth through efficiency, consolidation and restriction of the regulatory environment to locally established plasma procurement in order to control the major part of the worldwide market. On the other side, no one can contest the legitimate inspiration for developing countries to improve their standard of care through the valuation of their domestic resources. Beyond economic statement, there are also unaddressed scientific questions such as: is it proven that the immune diversity of relatively "antigen-protected" Western blood donors is better fitted to address the septic environmental challenge of the most remote worldwide patients than the own antibodies of these autochthon populations ? This could lead to a longer article. If the above divergence is to happen, the potential limits to product availability (or at least the feeling of full dependence on foreign suppliers) that it will induce in a growing number of countries should support the emergence of some well economically designed industrial projects by regional leaders, sanitary (and probably politically) linked to some broader regional interests for plasma supply. In my view, new facilities using well established technology and located outside of the competence of the Western agencies will be the future operators of profitable and successful contract manufacturing programs. Eligible countries for such industrial challenges are limited but partners for joining these programs with their domestic fractionation grade plasma resources are numerous around the world. In preparation for this new era, any country thinking about improving its global sanitary level should invest in blood transfusion and higher volume of well qualified plasma right now.

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