Review Article

Steps and challenges in the implementation of a plasma fractionation program: Brazil experience

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Abstract: In the year 2005, Brazil has decided to create a state-owned company for fractionating the country's plasma, and a society named Hemobras was put in place. The project took into account the plasma availability, local regulatory capability and the existence of an internal market for plasma derivatives. Transfer of technology process was initiated, with a foreign plasma fractionator, and a plasma toll fractionation was associated to the tech transfer, in order to accelerate, step by step, the technology incorporation. The main challenges regarding the project were related to engineering aspects, including elaboration of basic and detailed designs, since the country had little local expertise in this field. A mixed approach was used, consisting on hiring a specialized body of engineers as well as outsourcing national and international engineer companies. Manpower recruitment was another difficulty, because there were very few specialists in the manufacture of biological medicines and plasma fractionation. Hemobras has adopted a heavy training program to circumvent this issue. Finally, Hemobras developed a massive investment focused on improving plasma quality in a joint program with blood centers. This program was able to greatly increase the plasma availability in Brazil. Overall, installing a plasma fractionation facility is a very complex and expensive task, with many challenges to be carefully addressed.

Keywords: Plasma fractionation; plasma derivatives; transfer of technology

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Background

Since 1995, the Ministry of Health (MoH) had been massively importing factor VIII and factor IX concentrates as well as partially activated prothrombin complex to serve the country's entire population of persons with hemophilia who received (and still receive) these drugs completely free of charge. In addition, the network of public and private hospitals and clinics in Brazil also acquired—in a decentralized way, sometimes at a very high cost—intravenous polyvalent immunoglobulin (IVIg) and albumin.

In 2001, the MoH created a comprehensive program for the national blood system, which included empowerment of the National Blood and Plasma Derivatives Coordination and a substantial increase in resources to the blood program.

The local production of plasma derivatives was identified as one of the most important goals of the blood program. The decision to incorporate this objective resulted from a long discussion in the country about self-sufficiency in plasma derivatives. The fact that the country was spending heavily on importation of plasma derivatives, combined with the internal existence of plasma surplus, naturally brought to the discussion the pertinence of having a local production of therapeutic plasma proteins, or, alternatively, to initiate a toll fractionation program that would avoid the wastage of recovered plasma (1).

This discussion, which included stakeholders such as the Brazilian Society of Hematology and Hemotherapy, patients' advocacy associations, especially the Brazilian Federation of Hemophilia, directors of blood centers, the blood and plasma derivatives coordination and attorneys from several ministries, among many others.

The MoH took the final decision, which came out

in 2001: to carry out an international tender for the contract fractionation of Brazilian plasma, focusing on the production of four plasma derivatives—albumin, IVIg, factor VIII and factor IX concentrates. This tender was to be coupled to a working group constitution devoted to evaluating the alternatives for the construction of a plasma fractionation manufacturing plant in the country (1).

Two basic assumptions guided this decision: (I) the existence of a well-established internal market for plasma products, which was relatively strong and included direct importation, in great volume, by the MoH itself; and (II) the availability of recovered plasma of industrial quality, in a volume allowing to glimpse the operation of a factory in the country. This volume, at the time, was estimated at 150,000 liters of plasma per year.

The working group to analyze the possibility of building a plasma fractionation facility in Brazil would only be created in 2004, three years after the decision. The group's work was completed in September 2014.

Hemobras creation

The multidisciplinary working group put in place to study the creation of a plasma products manufacturing plant in Brazil, analyzed some main aspects:

(I) Legal framework required for the company;
(II) Technology to be used;
(III) Economics;
(IV) Plasma availability.

Legal framework

The main legal basis that guided the entire legal discussion of Hemobras was the Brazilian constitution (2), which establishes in its article 199 that "blood and its derivatives cannot be commercialized." Based on this premise, the jurists who worked in the task force considered that the company that would take care of Brazilian plasma fractionation could not be for profit, which excluded most of the major companies producing plasma proteins.

A model of concession or service provision, similar to the one adopted in Spain, Australia or Italy, where a private company receives the plasma from the country, produces the medicines required by the contractor and is remunerated for the services provided, was possible, according to the task force. In such a model, the drugs would return to the Brazilian MoH, which in turn would distribute them to public hospitals, free of charge.

However, the model chosen was the creation of a state-owned company, which would have the purpose of fractionating Brazilian plasma for producing plasma derivatives. The choice of this model took into account strategic considerations, including country self-sufficiency, issues such as the development of a biotechnology pole, country's mastering of a new technology, and the creation of qualified jobs.

It is important to add that, following the task force's attorneys recommendation, the MoH issued a decree stating that the surplus of plasma produced by the public blood banks was a property of the Federal Government.

Technology

It clearly aroused from the multidisciplinary group that Brazil did not master the sophisticated technology for the industrial fractionation of plasma. This, however, was not an insurmountable barrier to the project. The group considered that a transfer of technology from a foreign fractionator would solve the problem.

In the late 70's up to the 90's, Brazil had three very small plasma fractionation plants. Two of those plants produced only albumin, and the third one produced albumin and factor VIII. All three plants were shut down, mainly because they did not comply with good manufacturing practices.

They all used Cohn fractionation methodology, without any of the recent technology improvement, and with no automation. The one producing factor VIII concentrate used rudimentary chromatography techniques. Very few well-trained people worked at those companies and could help Hemobras project. This was an advantage, but it did not avoid the need for external information and massive support.

The development of proprietary technology, or the choice of producing only recombinant substitutes for derivatives for plasma products, was considered out of the question, especially because it would not be possible to predict how long the product development phase would take prior to licensing and commercialization.

Economics

All economic and financial feasibility studies showed that the project was economically viable, with a pay-back time of about 3 years, provided that the volume of plasma fractionated, initially 250,000 liters, could reach 400,000 liters by the end of the third operational year, and provided

that at least five different plasma derivatives were produced.

There were two main reasons explaining the rapid return on investment: first, the fact that plasma, owned by the Federal Union, would be sent to the company without the need to reimburse the supplying blood centers. Secondly, the fact the MoH was a captive market for plasma derivatives; it would absorb the totality of Hemobras production, thus promoting a considerable reduction on sales and marketing costs.

Plasma availability

The task force studies showed that there were in Brazil about 350–400,000 liters of recovered plasma that would be available for industrial fractionation. However, only 150,000 liters out of this amount would fulfill the regulatory authority and industry quality requirements for fractionation.

The group recommended that the MoH invested heavily in blood centers to rapidly increase the availability of plasma of industrial quality for fractionation; another recommendation was to increase the number of blood donations in the country, eventually implementing apheresis plasma collection from non-remunerated donors.

Final decision

After receiving the task force report, the MoH decided to set up a state-owned, not-for-profit-company. All the society shares would be a property of Federal Union. The law creating the company—the Brazilian Company for Plasma Derivatives and Biotechnology/Hemobras—was approved by the National Congress in December of 2004, and the company happened to exist from May 2005.

In parallel, the MoH launched a public tender for choosing a plasma fractionator to sign a toll fractionation contract to produce Factor VIII and Factor IX concentrates, IVIg and albumin from Brazilian plasma.

Challenges and barriers faced by Hemobras

Building and operating a plasma fractionation plant is a very complex task, especially in countries that do not yet master this technology. Even the decision to implement a plant of this type is complex, and subject to criticism, sometimes quite strong, of political, economic and technological natures.

Most of the criticisms of the Hemobras project—which occurred when the company was created in 2005—referred to the risk of technology obsolescence. At this time there were few recombinant substitutes for plasma derivatives on the market, but it was already clear that the portfolio of this type of drug would expand rapidly. There was also the criticism arguing that other types of treatment, which would dispense plasma derivatives usage, for diseases such as hemophilia A and B and von Willebrand disease, as well as for the treatment of conditions treated by immunoglobulins, would be available quickly.

It is beyond the scope of this article to describe or analyze critiques linked to political or economic concepts. What we will describe here will be the main effective barriers faced in the implementation of the project.

The main barriers observed were the following:

- Aspects related to engineering;
- Difficulties in technology transfer;
- Plasma availability;
- Requirements of Brazilian legislation regarding purchases and contracting;
- Regulatory aspects;
- Economical aspects;
- Human resources.

We will then address each of these difficulties.

Engineering

Brazil is a country with an expanding pharmaceutical industry, especially after the arrival of generic drugs. However, the complex of biotechnological pharmaceutical industries was—and it still is—very small in Brazil, except in vaccines area, where the country is self-sufficient.

The preparation of the basic and detailed designs for the construction of a plant for plasma derivatives requires a good expertise, which, in turn, implies an engineering team that knows the technology and has experience in the field. However, if the technology is not mastered by the country, the design elaboration becomes a very complicated task. One can, of course, look for foreign engineering companies, and Hemobras did so: the task of elaborating the basic and detailed designs was delegated, by contract, to the company in charge of the transfer of technology.

That is an alternative that also cause problems: companies outside the country may adopt engineering practices not always accepted in Brazil; besides, even if the design is prepared abroad, it still requires a critical mass of local engineers able of critically evaluating and reviewing them and to request the necessary modifications and

adaptations.

In some fields, such as civil or electrical engineering, this is relatively simple; however, for design aspects that pertain to the technology itself, such as automation engineering, equipment user's requirements, project acceptance requires an engineering know-how that is difficult to find. The recruitment of Brazilian engineers with expertise in biotechnological projects—for example, engineers with experience in classical pharmaceutical industry or in the vaccine industry—could be an alternative, as well as the recruitment, by Hemobras, of foreign engineers. However, Brazilian labour legislation imposes enormous obstacles to the hiring of foreign employees, making this option almost impossible.

On the other hand, since Hemobras is a company that belongs to the Brazilian state, it must follow the rules and laws that define the human resources recruitment. And these laws establish that (I) the only way to recruit people in public enterprises is through public selections, which in turn needs to be authorized by the presidency of the republic and (II) public companies are not free to define the salary of each professional category. They have to negotiate it with the Ministry of Planning, which has the final word. As Hemobras was just starting its activities, it was allowed, on an exceptional basis, to directly recruit a small contingent of professionals from outside the country.

Hiring a national engineering company with experience in pharmaceutical projects to advise Hemobras would be a third alternative, but it needed to be done through public bidding, which is never a quick process. All these difficulties resulted in delays in Hemobras project, so that lapse of time between the design contracting and its conclusion and acceptance, which would allow the facility construction, was 16 months—and still, because it was decided to initially contract the building of one of the six main blocks of the factory, the plasma warehouse, while the projects for the remaining blocks, more complex, continued to be elaborated.

There were other barriers linked to engineering; for example, the lack of local expertise for the elaboration of user's requirements designs for the customized construction of specialized process equipment, such as aseptic filling machine, process and utility tanks, large freeze-dryers, water treatment and other utilities, chromatography columns, virus inactivation units etc.

Another problem, already mentioned, was the lack of familiarity of foreign engineers with Brazilian standards. For example, in the country where the design was prepared, there was no need to build a water tower for this type of facility, whereas in Brazil it is mandatory; the ethanol tanks were buried, an unusual practice in Brazil and, above all, the degree of the details in basic and detailed design was much less than the one required by Brazilian regulation and practices.

Hemobras' strategy to mitigate this situation consisted on directly hiring a small team of engineers, hiring an advisory national engineering company and increasing the degree of detailing of the drawings, descriptions etc., in order to comply with Brazilian legislation, as well as to make the necessary adaptation to local standards.

The strategy was successful, even though the time required for launching the public tender for the facility construction took two years, which represented a major delay in the initial schedule. Regarding process equipment, however, the company had to rely almost entirely on the projects developed by the technology transfer company.

Transfer of technology

In the Brazilian case, the challenge began in establishing the *modus operandi* for selecting the partner in charge of technology transfer. Brazilian law does not allow free negotiation or direct choice of this partner; it requires, rather, a public tender, with very clear rules.

In order to carry out this bidding, it was necessary to pre-estimate the tech transfer price, obtained from similar contracts. Theoretically, this procedure would avoid high prices, above the standard; however, since there was no previous tender for the same purpose in the country, it was very hard to find comparison elements.

In addition, it was also necessary to insert a very detailed description of the services to be provided in the documents that would guide the bidding. This was another challenge: the transfer of technology in the plasma derivatives field consists in the transmission of industrial secrets and know-how, not in tangible items.

The elaboration of tender documents was a long and complex task: how to detail the services without excluding, *a priori*, one or more fractionators? If we put, for example, the C1-esterase inhibitor concentrate, or the fibrinogen concentrate among the plasma derivatives whose production technology was to be transferred, we would eliminate most of the potential bidders. If we require very high yields, or the application of certain viral inactivation/reduction methods, the same would occur.

Moreover, how can one define the completion of a

certain technology transfer step? For some items, such as drawing up a conceptual design, it was simple. For other items, however, this was much more difficult. How to determine if a particular *savoir faire* was not successfully transferred due to a fault of the transferring company or to a fault of the receiving company, whose team was not competent or skilled enough? What would be the criteria to be established by the tender documents to determine that the service had been provided, and the contracted company should be paid for the execution of the task/service?

This range of difficulties made the preparation of tender documents time-consuming; it took a few months to produce, and it resulted, at the end, in a small booklet containing all the guidance, specifications, technical and legal requirements for the bid. We sent the book to all the potential candidates (3).

Estimating a fair price for the transfer of technology was another major drawback, since it was a transfer whose specific content was unprecedented in the country. The estimated price for the global services, which represented the upper limit to be proposed by competing companies, has become very low, leaving most of the eligible companies out of the competition.

Despite these difficulties, the bidding was successful, and a transferring company was hired. Then, the process of technology started, plenty of small conflicts, misunderstood and conceptual disagreements between the transferring and the receiving company—but this was more than expected, since it does happen in the vast majority of technology transfer processes (4).

Plasma availability

At the moment Hemobras was created, there were around 150,000 liters of plasma available for the industry, although a total surplus of more than 400,000 liters were available in the country.

Hemobras and the MoH developed together a program aiming to increase the working quality of blood centers. This program included workshops for blood centers, focused at in people from blood component preparation and storage, quality control, quality assurance and plasma freezing. Blood centers educational audits were also performed by Hemobras assessors (5).

Hemobras bought and provided to the main Brazilian blood centers 70 blast freezers, in order to improve Factor VIII recovery, many automated and centralized systems for temperature control and many regular freezers and blood refrigerators.

Hemobras also made the decision to reimburse some costs incurred by the blood center in order to improve the plasma quality; it was an almost symbolic reimbursement, but it had a great effect, and the action was very well received in Brazilian network of blood centers (6). The partnership between Hemobras and the blood centers became much stronger after that.

As a result of all these initiatives, the availability of plasma for fractionation increased from 150,000 liters to 300,000 liters in a period of 2 years.

Human resources

From the beginning of the Hemobras project, it was clear to everyone that the issue of human resources would be a key element for the success of the project. We have already approached the specific Engineering point; however, this was not the only bottleneck regarding the provision of human resources for the operation of the Hemobras plant, from the design and construction phases up to the operation phase itself.

The availability of specialists and technicians necessary to a plasma derivatives plant—chemical engineers, pharmacists, biotechnologists—is very short in the Brazilian market. Equipment qualification and operation, process validation, industrial plasma fractionation, chromatographic protein purification and, finally, specialists in industrial automation: all of that represented challenges for finding and hiring the adequate professionals. Besides, there was, and still is, a strong competition by these professionals; this competition included oil and gas industry, which was booming in Brazil and traditional pharmaceutical industry.

Moreover, Hemobras could only recruit its staff through a public selection with very strict rules, where previous experience was not allowed to be an asset; the salaries were pre-established, with no liberty to free negotiation.

To circumvent this pitfall, Hemobras organized a training of people hired after the public selection, in the facility and in the country of technology transfer company. In total, 28 people were to be trained; this training was scheduled to range from 3 months up to 1 year. This training was an obligation stipulated by contract.

This palliative solution had also risks and difficulties. The risk was to see the trained professionals being absorbed by the private pharmaceutical industry, or even by the oil and gas industry, upon their return to Brazil, since these companies are free to propose salaries and negotiate

contracts with their employees.

Another issue was the language: all the trainees had to be fluent in French before traveling, which forced Hemobras to finance courses in this language for its trainees. The training timing was also very complicated; it had to be done well in advance so that people were already trained at the time of the implementation of a given process. However, if the training were completed long before the operation, there would be a risk that knowledge, experience and acquired skills will gradually fade away before the trainee could put their hands on.

Regulatory aspects

The Brazilian Regulatory Agency—ANVISA—already had, at the time Hemobras was constituted, a great experience with plasma products. This experience came from the follow up of previous contract of Brazilian plasma toll fractionation, and from the inspections that it has been carrying out, since 2001, at the majority of worldwide plasma derivatives industry. A highly qualified body of inspectors was created, with a great theoretical knowledge of main aspects related to the production of plasma products (7).

Thus, this point, which may constitute an important pitfall to the success of a project to build a plasma-manufacturing plant was not an a priori problem for Hemobras. The great unknown about the regulatory part was—and still is—the need for clinical studies for the blood products to be produced by Hemobras. Several other regulatory agencies in the world face this issue. In the case of Hemobras, the company's opinion was that such studies would not be necessary, since the plant would only reproduce the way of manufacturing at an existing plant, whose products had all been submitted to clinical studies, before being registered in the country of origin and in Brazil.

There were differing opinions in the country, and the debate in this respect was relatively intense. Progress in the regulation of biosimilar medicines worldwide will likely make this discussion sterile, and clinical studies will not be required by ANVISA.

The path should be that of the requirement of bioequivalence studies, for situations of transfer of technology. Countries interested in implementing a national capacity for plasma fractionation should always take this variable into account and discuss with the local regulatory agency on the need for clinical studies. This is really a critical point: if the regulatory agency requires clinical trials, this will considerably slow down the implementation schedule, and it will make the project much more expensive.

Legal aspects

The two main issues arising from the legal aspects were the very strict Brazilian law about public contracts, and the restrictions regarding human resources.

The law about public purchases requires that state-owned societies perform all their acquisitions through public bids. Organizing a public bidding following the legal procedures is a slow process, requiring a series of rituals and steps. It is not an insurmountable obstacle in itself; it can, however, cause many inconveniences for the operation of a factory. Assuming that a certain machine, essential for production has broken down and needs to be replaced, Hemobras can only do so through a public bidding process. To avoid interruption in production, the solution would be to make an emergency purchase, which follows a faster ritual, but it is still not an immediate process.

Another major obstacle from the law occurred in the acquisition phase of large process equipment. The technology transfer agent claimed that for some equipment, the same brand used in his factory should be purchased, to facilitate qualification, process validation and training, as well as to guarantee results similar to that of the parent plant. This, however, is not accepted by Brazilian law, which requires a public selection, in which equipment of other brands, sometimes unknown by the technology transfer company can win the tender. This is clearly another major difficulty for the country's implantation of a plasma-manufacturing plant.

The other legal problem with a direct impact on the project concerns the prohibition of free choice of human resources, which was already discussed in a previous item. The replacement of people is never fast; if an employee quit the company, there should be a formal summons process that can last more than 30 days, which can imply that some activities must be temporarily interrupted.

Economic aspects

As with any major project, ensuring the necessary financial resources is always of paramount importance. Hemobras project is not different, and it is even a little more difficult, because of the very high costs involved.

Although Hemobras' resources were allocated in the federal government's multiannual budget, the risks of lacking money are always present. Some factors contribute

a lot to this, in this type of facility building, and should always be taken into account by the managers of this type of project.

The first aspect is that there is a trend to underestimate costs, maybe because they are very, very high, when compared to the standards of a traditional pharmaceutical industry.

The second aspect, which is not always taken into account, is the risk that the project timeline will not be met, particularly when there is a transfer of technology involved, which always brings many uncertainties about deadlines. Synchronization between the various steps—design, civil works, purchases, construction and installation of utilities and process equipment, qualification etc.—is also a very complex aspect, very difficult item to be fulfilled without fails leading to compromise the whole schedule.

There is also a trend to underestimate the total time until the factory becomes operational; it is always a long time, hardly less than 6/7 years and it can easily reach eight or more years. Disregarding this fact makes economic-financial feasibility studies unsuccessful and requires budgetary supplements, which generate political wear and discredit for the project.

Conclusions

In principle, the Brazilian project for local plasma fractionation was fulfilling all the requirements. Despite of that, many challenges for a successful implementation had to be faced; some of those challenges and barriers were forecasted from the beginning, but many others were unexpected.

The majority of those challenges are probably the same as the ones faced by any other country in the same situation. Based on Hemobras experience, we consider that some strategies can facilitate the task of implementing a plasma fractionation facility.

A very careful and detailed analysis of the legal framework and its impacts on the project will forecast some problems and difficulties, as well as the possible pre-emptive interventions to avoid or circumvent these obstacles.

The engineering issue, one of the most constraining for this type of project, can be mitigated by an intensive and timely training program. This program should be included in the contract as a technology transferring company duty. If possible, some mechanism for retaining these trainees upon their return should be applied. Hiring a local engineering company with some expertise in pharmaceutical industry (and biotech industry, if locally available) is also a very helpful tool.

The human resources recruitment must comply with local regulation and laws; if these regulations are too strict, some contour solution should be anticipated from the beginning of the project. In Brazil, we had to negotiate, with the supervisory bodies, and get special and temporary authorization for hiring people for strategic jobs without the need of a public selection. Outsourcing and, again, a very powerful training program for people hired by a public selection can be viable alternatives.

For the regulatory aspects, Hemobras strategy was to have a previous and close discussion with our regulatory agency, in order to avoid mistakes and unacceptable design for the project. In Brazil this was facilitated by the fact that the MoH and ANVISA had decided to create a joint committee to discuss regulatory issues related to all the new biotechnology products being developed in the country (8,9).

Transfer of technology is always a very difficult and tense process; nevertheless, we still believe that this is the simplest and the fastest way to obtain the plasma fractionation technology. Coupling the plasma fractionation facility implementation with a toll fractionation, necessarily with the same foreign company, is an option that can greatly facilitate the project development. This strategy allows the team to put their hands on very soon and to start several activities much earlier (10).

In summary, installing a local plasma fractionation capacity is very complex, with many pitfalls and bottlenecks; risk analysis and risk mitigation measures can help to circumvent the challenges, as well as well target-based strategies. Working very closely to the blood centers is also a very commendable practice.

Hemobras has adopted many of those strategies, most of time successfully. However, the full plant is still not operational, due to supervenient contractual disagreements between Hemobras and the building company which was in charge of the construction.

The building works were stopped three years ago, when around 75% of the plant was completed (*Figures 1-3* show Hemobras facilities). So far, an automated plasma cold chamber is ready and operational, as well as the quality control laboratory building. The remaining areas are expected to be completed one year after the works resume.

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Figure 1 Hemobras global view.

Figure 2 Hemobras plasma warehouse building.

Figure 3 Hemobras plasma warehouse—internal view.

Footnote

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