

# Information Sheet

## Plasma Contract Fractionation Program

### General considerations

The provision of safe and sufficient plasma derivatives to meet the needs of local populations in all countries requires special consideration and a well designed technical and economic support.

Options include importing finished products and/or procuring products made from locally collected plasma.

One approach is to consider local fractionation of plasma by building and operating a plasma fractionation facility or a regionally supported facility. Such a facility may produce finished products, or may produce intermediate products that are further manufactured in another facility.

An alternative approach to ensure availability of plasma products is the implementation of a plasma contract fractionation program where:

- Local plasma is sent to one or more established fractionators, and the plasma is fractionated following pre-agreed terms
- End products are returned in all or in part to the country of the supplier of plasma.

The costs involved in establishing a contract fractionation program are substantially less than those involved in establishing and operating a fractionation plant. In the absence of a local fractionation plant, products originating from plasma collected locally can be made available using contract fractionation in a shorter time frame.

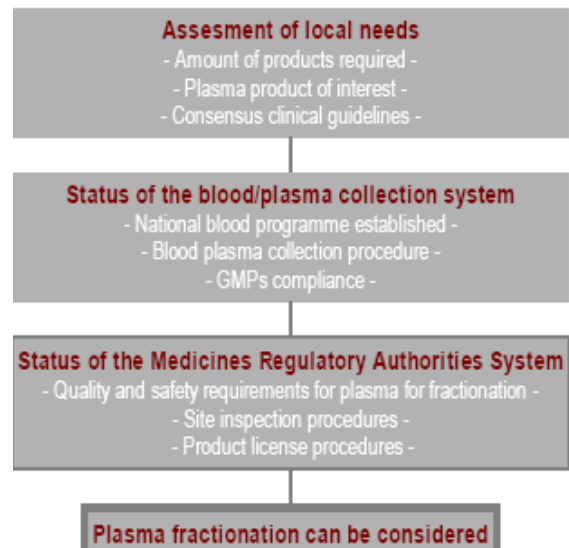
A plasma contract fractionation program may serve, under certain circumstances, as an initial step prior to switching production to a locally built facility. This lapse of time may then be used to reflect better on the rationale of building a local facility, to expand the plasma collection potential, and to permit appropriate design, qualification and validation of the facility, as well as training of local personnel.

The critical parameters when considering the approach of a plasma contract fractionation program are further discussed in this document.

## Points to Consider

A careful and precise decision-making process must accompany any decision to embark on a plasma contract fractionation program. Although in line with those requirements ensuring a safe and cost-effective production of blood components, there are additional specific needs associated to the manufacture of plasma products that should be considered. These are:

- ❑ A careful assessment of the clinical needs and trends and a clear definition of the type and quantity of plasma products required for an appropriate treatment of patients.
- ❑ A sufficient blood/plasma donor population, nationally or regionally, to guarantee an adequate sustainable supply of safe source material for fractionation.
- ❑ The existence of a mature blood collection organisation co-ordinated nationally. Blood/plasma donor selection, collection procedures, testing methods, donation handling, storage and transportation of plasma should follow defined quality assurance procedures, as highlighted by international guidelines.
- ❑ Plasma for fractionation should meet the quality and safety criteria necessary as a source material for the manufacture of plasma products. It should comply with the requirements of the fractionator and that of the medicines regulatory authorities involved. Ensuring the traceability of plasma between blood plasma donations and final plasma products is a key element to consider.
- ❑ A national competent professional advisory structure with sufficient level of local expertise to make recommendations on the program be involved in a decision making process.
- ❑ A national Medicines Regulatory Authority (MRA) able to assess, and regulate the complex issues associated to the quality and safety of human derived medicinal products.
- ❑ The economic balance of the whole program should be carefully evaluated, to make sure that the program, covers the various cost parameters to be cost-effective.



## **Feasibility Evaluation**

A plasma contract fractionation program should be based on the principles of a pharmaceutical contract manufacture and arrangements should include the relevant requirements established by the national medicines regulatory authorities. The responsibility and duties of each party involved in this contract (including plasma suppliers and fractionators) should be clearly defined in specific technical documents. Parameters to consider include:

### ***Source of plasma supply***

A plasma contract fractionation program should be envisaged only if there is a guaranteed continuity in the plasma supply. In many cases where the availability of plasma is only temporary it is not advisable to envisage entering any such agreements.

The potential to use plasma obtained from whole blood donations, and the possible need to collect plasma by apheresis procedures should be evaluated.

### ***Plasma volume***

A minimal continuous supply of plasma for fractionation is required prior to considering a plasma fractionation contract. Plasma fractionation agreements often involve a yearly minimum volume of at least 30'000 litres. However, examples exist where long-term agreements are carried out with lower volumes from centralized organisations. Technically, the minimum acceptable level depends on the batch size at two different levels: (a) at the stages of plasma pooling and bulk fractionation processing (typically from 1000 to 4000 litres per batch), and (b) for the finishing of the plasma products, since intermediate fractions from multiple plasma pools from the same origin may be combined.

### ***Duration of the agreement***

A guarantee should be obtained that the fractionator can commit to the contract for a minimal agreed period of time, in compliance with the requests of the supplier of plasma. If the volume of plasma is sufficient, it may be wise for such countries to contract with more than one plasma fractionator to provide flexibility and there by help to ensure continuity and diversity in the supply of products.

### ***Product profile and characteristics***

The general principles of plasma fractionation are well established and implemented in similar ways. There are however numerous variations involved in the production of plasma derivatives. Viral inactivation methods and batch size may have an impact on the product yields. Therefore they should be considered when negotiating a contract with a fractionator and taking into account the relevant regulations.

Moreover, developing countries may encounter economic constraints or patients' population characteristics that prevent them from adhering to the same clinical approaches as for developed countries. For instance, dosage forms used for blood coagulation factor VIII concentrates and intravenous immunoglobulin (IVIG) preparations may, at least initially, be smaller than those used in more medically advanced populations. The potential trends in product consumption and the possible impact of other therapies and technologies should also be assessed for appropriate planning.

## Regulatory requirements

The plasma contract fractionation activity involves different parties aiming to ensure the quality and safety of the source material, the plasma for fractionation, and the final products.

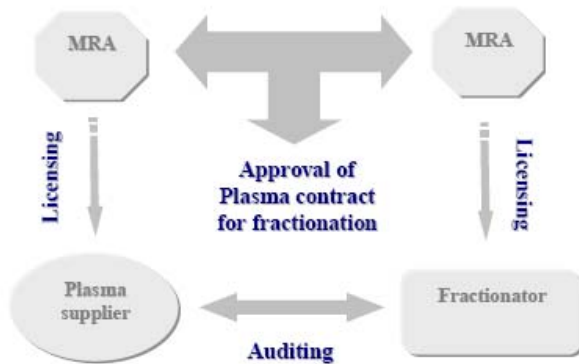


Figure 2: Parties involved in a contract plasma fractionation program

### Blood/Plasma collection procedures

Prior to being considered as the starting material for medicinal products, plasma from all collection centres needs to meet quality requirements that can be demonstrated through specific auditing and inspection procedures according to GMP.

#### Plasma supplier: audit and inspection

Considering that the collection of plasma for fractionation forms a crucial part of the manufacturing process of plasma derived products, the following information should be available:

- ▶ epidemiological characteristics of the donor population
- ▶ blood/plasma donor selection criteria
- ▶ collection and testing procedures
- ▶ processing, storage and transportation methods

This information must meet the acceptance criteria of the national MRA in the country of origin of the plasma and the fractionator. In turn the fractionator must comply with the plasma criteria of the NMRA in their own country.

The approval process abovementioned is based on the quality criteria that are pertinent to plasma for fractionation. As a consequence, a situation may arise where collection centres may satisfy requirements for the collection of labile blood components used locally, but not for the collection of plasma for fractionation. Similarly, the important criteria for donor testing may be fulfilled, but noncompliance criteria may be found on logistical aspects like separation times, freezing, storage and transport conditions.

### Plasma Fractionation Procedures

Its own national medicines regulatory authority should license the fractionation facility.

It is advisable, that the regulatory authority of the plasma suppliers assesses the quality and safety of the fractionation process prior to the establishment of the contract.

One of the first steps that should be taken before deciding on the fractionation is to verify that the plasma products manufactured by the intended contract fractionator are all virally inactivated and the product license is completed.

Depending on specific national policy, an inspection in advance of the product licensing procedure of the facility where the fractionation of plasma would take place may be needed. This inspection may be performed, for instance to determine how batch segregation between plasma from different origins is ensured. Such inspection should be done in coordination with the respective regulatory authority responsible for granting the license to the fractionator.

Other relevant aspects to be considered as general background may include the following, which are given only as examples:

- Country where license was granted
- Regulatory history
- Review of previous audit reports

### ***Product Registration***

A situation may arise whereby, the terms of contract fractionation agreement authorise the plasma fractionator to keep some/part of the products obtained from the fractionation process. This occurs when products would be in surplus in the country of origin of the plasma, or when this arrangement allows reducing the fee charged for fractionation.

The holder of the products resulting from the contract plasma fractionation activity should comply with local marketing authorization requirements and fulfill local licensing procedures. The whole licensing procedure may include a plasma master file, a site / establishment master file, and the individual products registration files. As indicated above, this licensing procedure may require specific inspections of the facilities used for collection of plasma and for its fractionation.

As stated above, a relevant national Medicines Regulatory Authority (MRA) should regulate plasma products. Any entity involved in the distribution of blood plasma products should comply with the local requirements for the storage, distribution, and traceability of medicinal products when handling plasma derived products.

## **Economic considerations**

Although it is not the objective of this fact-sheet to review the economic aspects pertaining to a contract fractionation agreement, the following points can help to estimate the economical viability of a program, taking into accounts elements that contribute to the cost of the plasma products:

- Collection cost of plasma, including donor recruitment
- Testing procedures on single donations
- Storage of plasma
- Transportation of plasma (by sea or by air, depending upon circumstances) to the fractionation facilities
- Cost for serology and NAT testing as required
- Fractionation charge per unit of product made (e.g. per g of albumin and IgG, and IU of FVIII and FIX), or per litre of plasma fractionated. A minimum guaranteed yield may be associated to the charge
- Shipment of the products to the country of origin
- Plasma product registration costs
- Distribution costs
- Clinical and marketing/sales expenses, administration and overhead charges

Usually, the price of plasma and processing fees represent the two single major components of the overall cost of the products. The cost of plasma depends on two factors: one, on whether recovered plasma resulting from a collection program driven by red cells needs is available. This could allow for significant cost sharing, or two, on whether a specific collection program of plasma for fractionation is introduced.

Processing fees charged by the fractionators are based on criteria that include the total volume of plasma processed, the batch size at the stages of plasma pooling and end-products finishing, the number of products made and the recovery. The purification

technology and the viral inactivation methods influence recovery or yield of plasma derivatives. Royalties to third parties who own production technology may be required. Distribution and marketing costs depends upon local elements, such as whether the blood transfusion network is involved in the distribution or whether a distinct distributor is hired.

## References

- ◆ WHO Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives. WHO Technical Report Series No. 840 (Annex 2).
- ◆ Guide to the preparation, use and quality assurance of blood components. 5th Edition. Council of Europe
- ◆ WHO Guidelines for National Authorities on Quality Assurance for Biological Products WHO Technical Report Series No. 822 (Annex 2).
- ◆ Regulation and licensing of biological products in countries with newly developing Regulatory Authorities. WHO Technical Report Series No. 858 (Annex 1).
- ◆ Good Manufacturing Practices for pharmaceutical products. WHO Technical Report Series No. 823 (Annex 1)
- ◆ Good Manufacturing Practices for biological products WHO Technical Report Series No. 822 (Annex 1)
- ◆ EU Guide to Good Manufacturing Practices, Annex 14, <http://pharmacos.eudra.org>
- ◆ PIC/Scheme Good Manufacturing Practices: <http://www.picscheme.org>



Quality and Safety of Plasma derivatives and Related substances  
Department of Medicines Policy and Standards