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CONTRACT FRACTIONATION

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Treatment for All

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Table of Contents

Preface

This monograph is the fifth document in a monograph series entitled "Facts and Figures." The first four issues of the series discussed blood products in general, the organization of national programs for comprehensive hemophilia care, the production of single donor cryoprecipitate and of intermediate purity products, and viral safety issues. The series aims to provide decision-makers with basic data and knowledge to help them make the most suitable choices regarding hemophilia care.

The present document was compiled on the basis of the best available information of a general nature. No important decision should be taken without a thorough analysis of local conditions.

The definitions of words printed in bold type are included in the Glossary of Terms at the end of the monograph.

Acknowledgements

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Thierry Burnouf of Human Plasma Product Services reviewed and extensively revised this edition in 2004 and 2008.

Contract Fractionation

The World Federation of Hemophilia

1. Introduction

There are four possibly complementary ways of ensuring a national supply of factors VIII and IX concentrates and other hemophilia products:

- Local production of single-donor or small pool cryoprecipitate (factor VIII) and possibly cryo-poor plasma (factor IX) (with the drawback that those products cannot currently be properly viral inactivated) [1];
- Local manufacture of plasma products, including factors VIII and IX concentrates, from local plasma;
- **Contract fractionation**, whereby plasma is collected locally and processed in an independent facility, usually located abroad, and products are returned to the country;
- Import of factors VIII and IX concentrates.

Regardless of the options selected, a good medical infrastructure is needed to ensure that products are used effectively and efficiently, and to correctly assess the clinical needs.

This monograph specifically discusses contract fractionation programs. It covers the fundamental requirements for considering a contract fractionation agreement; the process of fractionation and the types of plasma products made available through fractionation; the various possible types of agreements between national health officials and foreign fractionators; and the technical, regulatory, and economical considerations for a successful contract plasma fractionation program.

2. Points to Consider for a Contract Fractionation Program

Contract fractionation may be considered only when strict requirements in the quality of local plasma are met. The cost and the capacity of collecting plasma for fractionation to meet the safety standards required by regulatory agencies and by fractionators must also be evaluated carefully. In this context, National Regulatory Authorities (NRA) play an important role in setting up and enforcing local regulations for the collection, testing, and storage of plasma for fractionation, in accordance with **good manufacturing practices** (GMP). Both the local NRA and the foreign plasma fractionator will usually need to perform inspections and audits of the collection centers to verify that quality requirements are met. The recently published WHO recommendations explain all the requirements needed for the collection of plasma for fractionation [2].

2.1 Plasma safety

Adequate provision of plasma meeting the quality requirements for fractionation must be ensured. A prerequisite is a mature, nationally coordinated blood program under the responsibility of a centralized blood collection organization. Such an organization should be certified by an independent authority to collect plasma for fractionation with adherence to GMP, within the frame of a quality system [3], and in compliance with the requirements of the fractionator.

In particular, good epidemiological control of the population where plasma is collected must be in place to follow incidence and trends of infectious diseases. Recommendations on epidemiological control of donor population can be found in a document from the European Medicines Evaluation Agency [4]. In addition to standard screening tests, testing strategies specific to plasma for fractionation (e.g. nucleic acid testing for relevant viruses) may need to be implemented if justified.

2.2 Plasma quality

The collection of plasma for fractionation requires specific measures for blood cell separation, freezing, and management of the cold chain. Additional freezing space and a central warehouse may be needed. Logistics for the transportation of plasma from the collection center to a central warehouse and to the fractionator is needed. Each plasma centre must provide agreed-upon documentation to certify

compliance with local regulations and plasma fractionator requirements.

2.3 Quantity

In principle, a contract fractionation program requires a minimum volume of plasma, ideally 30,000 to 50,000 liters (L) per year.

However, there are examples of contract fractionation agreements for volumes of 10,000 L or less. This may have technical and economical drawbacks, as small plasma and product batch sizes may have to be processed.

A guarantee of continuous plasma supply is important. Spot plasma fractionation contracts are, in most situations, not feasible, and usually not appealing to plasma fractionators, considering the heavy regulatory workload required.

Larger volumes (200,000 L and more) restrict the number of companies with sufficient capacity. Contingency plans are needed to reduce risks of product shortage in case of problems at the selected fractionation plant.

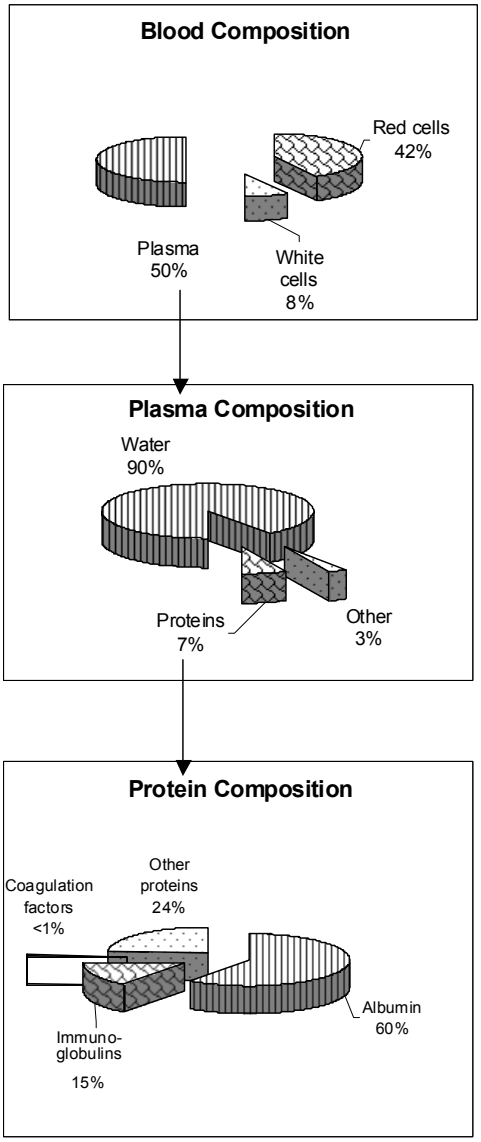
3. Blood Products

Blood has three types of cellular components – red cells, white cells and platelets – and a liquid component called plasma. Plasma can be used for transfusions or to produce cryoprecipitate or **coagulation factors** such as factors VIII, IX, prothrombin complex, and von Willebrand factor.

Plasma is also used to make other blood products, which are in increasing demand for the treatment of other conditions. In addition to coagulation factors, the most commonly used plasma components are **immunoglobulins, albumin, fibrin sealants, and alpha 1-antitrypsin**. The process of separating the plasma into its different components is called fractionation.

Plasma for fractionation can be obtained either by centrifugation of whole blood, or by apheresis procedures (where only plasma is retained and the blood cells are returned to the donor)

3.1 Blood composition



3.2 Main plasma products, their use, and typical commercial yields per liter of plasma

Plasma Products	Typical Indication	Industrial Av. Yield *
Coagulation Factors		
Factor VIII	Hemophilia A	100-200 I.U.
Factor IX	Hemophilia B	250-350 I.U.
Factor XI	Factor XI deficiency	
Factor XIII	Factor XIII deficiency	
von Willebrand Factor	von Willebrand disease	90 – 200 I.U.
Prothrombin complex concentrate (PCC, PPSB), factors II, VII, IX, X	Complex liver diseases, warfarin or coumarin derivatives reversal, inhibitors to factor VIII, hemophilia B**	300-500 I.U.
Fibrin glue (fibrin sealant)	Numerous surgical uses to achieve sealing, hemostasis, or healing of tissues (topical applications)	
Immunoglobulins (IgG)		
Intramuscular IG (IMIG)	Infection prophylaxis (e.g. hepatitis A, rubella, and other specific infections)	3-5 g
Intravenous IG (IVIG)	Replacement therapy in immune deficiency states, immune modulation in immune disorders	3-5 g
Hyperimmune IGs (either IM or IV)	Anti-tetanus, anti-Rhesus, anti-hepatitis B, anti-rubella, anti-cytomegalovirus, anti-varicella/Zoster, anti-rabies	
Others		
Albumin	Emergency volume substitution, shock, burns	22-28 g
Naturally occurring **inhibitors** (e.g. antithrombin)	To prevent certain types of pathological blood coagulation	

*Amounts indicate average yield per litre of plasma. Yields vary considerably according to the manufacturing process.
** When purified factor IX is not available

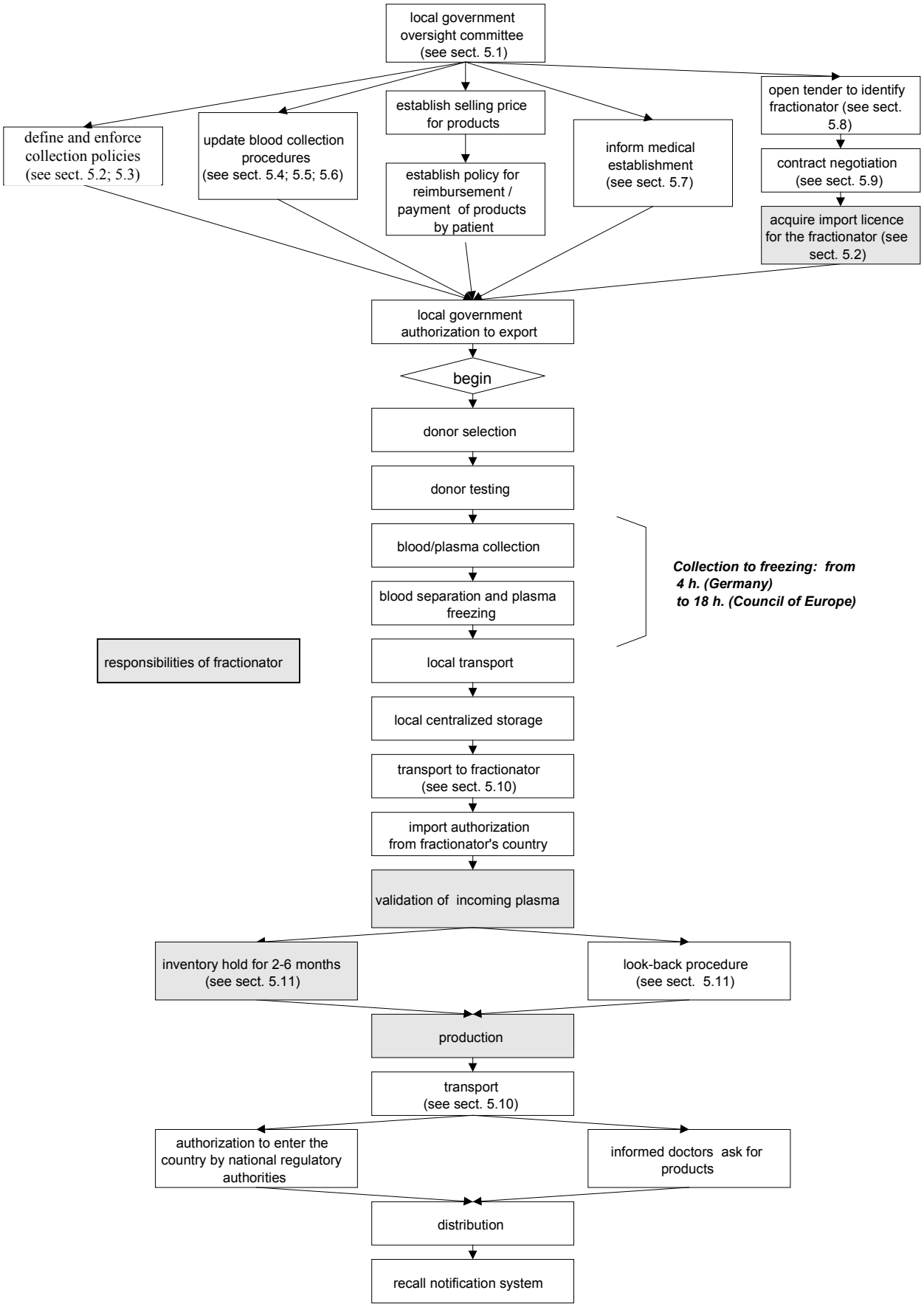
4. Contract Fractionation

4.1 Pros and points to consider

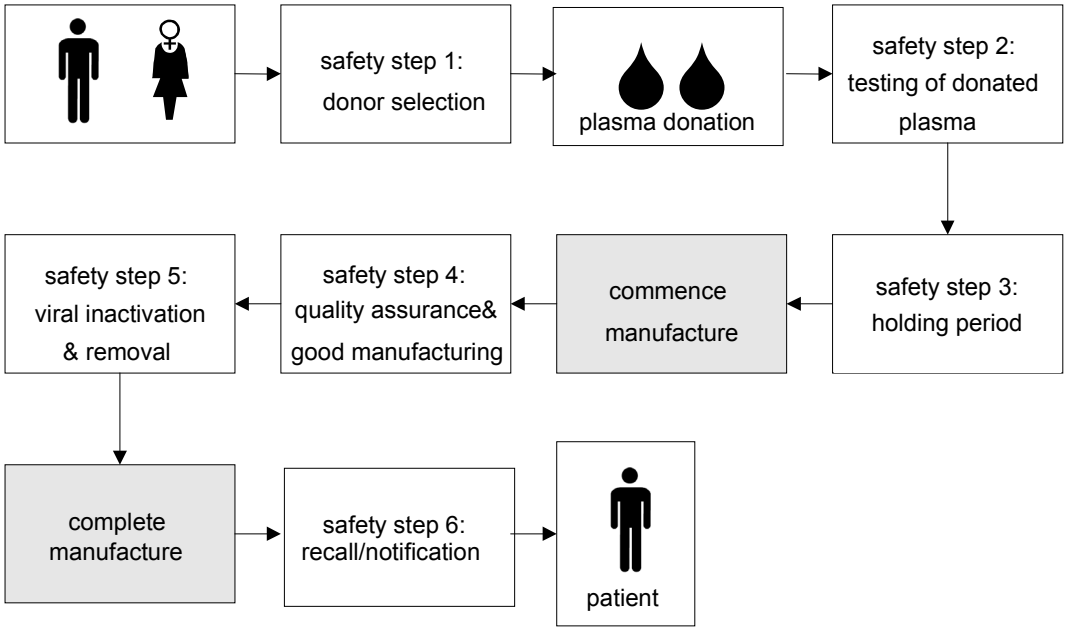
Contract Fractionation: Pros
• Relatively short-term access to products from local plasma, without the capital costs of building a fractionation plant. • Flexibility, as possibility exists to switch to another contractor. • The national supply is maintained during global shortages or for security reasons. • The source of plasma is known. • Leftover plasma from blood transfusions is not wasted. • Contract fractionation may improve the national blood/plasma collection system if the fractionator requires and enforces rigorous collection practices standards.

Contract Fractionation: Points to consider
• The blood collection system must already be well developed, preferably centralized, and have rigorous control systems. • Local technical expertise is valuable to understand the complexity of the quality and safety issues involved. • The cost of a plasma fractionation program is not limited to the fractionation fee but also includes the incremental cost of the collection of plasma for fractionation and logistical aspects (storage, transportation). • Technical problems arising at the fractionation plant can cause serious shortages of product if a contingency plan is not in place. • Contract fractionation may restrict the number of products available and limit clinicians' therapeutic choices. • The program may generate hostility from plasma product importers. • The amount of plasma collected may dictate the total supply of factor instead of being driven by clinical need. • A close liaison between the collection organization and the fractionator must be established to optimize the value of the contract fractionation program (yield improvements, efficiency, etc.).

4.2 Key steps in contract fractionation



4.3 Key steps in fractionation safety



5. Requirements of Contract Fractionation in the Country of Origin

A contract fractionation agreement is a contract between health officials, a blood collecting organization or another entity, in one country and a fractionator usually operating in another. Such a contract is a pharmaceutical processing contract and should therefore clearly define the legal obligations of each party in the performance of the terms of the contract. In particular, there are requirements to be met by the country of origin, such as plasma quality and quantity, and delivery schedule.

5.1 Contract oversight committee

The contracting country should establish an independent oversight committee (advisory committee) that establishes the overall guidelines and objectives of the program and ensures that the plasma provider and the fractionator comply with all aspects of the contract, including quantity, quality, processing methods (including batch segregation if required), safety profiles, and specifications of the products.

5.2 Quantity, quality and safety

In established plasma fractionation centres, the standard **batch** size at the stage of pooling is 2,000 L or more. A minimum of 1,000-1,500 L of plasma (about 5,000-15,000 whole blood donors or 1,700-6,000 apheresis donors) per batch is required. In general, the larger the batch, the better the return in terms of bottles of finished product per litre of plasma processed.

5.3 Regulatory issues

A contract plasma fractionation agreement involves specific regulatory requirements to ensure that GMP are met at all steps. As mentioned in section 2.1, the starting plasma must be collected by organizations that follow GMPs and are licensed by local regulatory authorities. The local plasma collection organization should be audited by the fractionator to verify its ability to collect plasma for fractionation, as well as to meet its requirements. An approval from the foreign NRA overseeing the fractionator is also generally required. Sometimes, an inspection of the collection centres by the foreign NRA may be conducted, if excess products are retained for sales by the fractionators in its country. Plasma products made from local plasma may need to get a specific registration, even if the same products from foreign plasma are already licensed by the local regulatory agency. The local regulatory authority may inspect the fractionation plant.

5.4 Plasma collection policies

Many national and international bodies, including the World Health Organization, recommend that blood and its products be obtained from unpaid (unremunerated) donors. However, because of the difficulty in obtaining a sufficient quantity of blood through unpaid donations, most of the world's present supply of factor VIII and IX concentrates is made by commercial companies with plasma collected from paid donors. A decision should be made on whether or not to use paid donors.

A decision should also be made concerning the use of **plasmapheresis** to obtain more plasma, independently from the collection of whole blood driven by the need for red cells.

5.5 Selection of plasma donors

Viral inactivation steps introduced during plasma product manufacture provide an excellent means to destroy viral infectious agents. However, plasma product safety also depends on a safe and efficient blood collection system that ensures:

- Careful selection of plasma donors;
- A safe donor base comprising donors with a known medical history;
- The exclusion of individuals with risk behaviours;
- Full traceability between donors, individual blood/plasma units collected, and the final plasma products manufactured.

5.6 Suitability of plasma

Plasma must meet certain criteria in order to be suitable source material for fractionation.

- It must be collected under aseptic conditions in a closed system (with absolutely no exposure to air) to maintain sterility and absence of pyrogens.
- Containers must comply with current requirements for blood containers.
- Each donation must be tested separately, using validated methods, for the absence of HIV-1/HIV-2-Ab, HBsAg and HCV-Ab, using test kits approved by the regulatory authorities of the country of origin as well as the country of fractionation. Some countries require the measurement of liver enzymes (ALAT/ALT), and most countries perform a syphilis test. Known authorities that regulate the testing requirements include the European Medicines Evaluation Agency (EMEA), the Paul-Ehrlich Institute (PEI – Germany), and the U.S. Food and Drug Administration (FDA – U.S.A.).
- Reactive donations must not be used for fractionation.
- The plasma must be kept frozen at a temperature below -20°C or -30°C, depending upon legal requirements and/or fractionators' specifications.

5.7 Donor requirements: general standards

Donors	• Healthy • Age criteria are country-specific (e.g. 18-65 years old) • Normal hemoglobin levels
Exclusion criteria	• Infectious disease (malaria, TB, etc.) • Drug abuse • Risk factors for HIV, HBV, HCV, vCJD
Temporary suspension	• Medication (anticoagulants, etc.) • Pregnancy • Transfusion • Surgery • Contact with hepatitis B • Travel to countries at risk for infectious diseases
Volume of donation permitted	• 400-500 mL whole blood*
Frequency of donation permitted	• Once every 8 weeks, 3-5 times per year (whole blood)*

* Medical limitations vary from country to country. Small donations (200 ml) may be collected in some countries

5.8 Transportation

Transportation can be done by truck, boat, or plane. Plasma must be shipped frozen at or below -20°C. Conditions for shipment are regulated and should be specifically mentioned in the contractual agreement and be in

conformity with current regulations. Temperatures must be recorded throughout storage and shipment, and each container must be labelled according to the contractual agreement. Agreed-upon documentation must accompany the shipment to certify compliance with the terms of the contract and relevant regulations.

5.9 Holding period

Donations may be stored for an inventory hold for 2-6 months according to the policies of individual fractionators, and as defined in the contractual agreement. The goal is to make it possible to eliminate a donation from an infectious donor in an infectivity window period, where screening tests are still negative. If it is learned that a donor has seroconverted or has developed a blood-transmissible infectious disease, all donations from that donor can be removed from the inventory prior to the manufacturing process. A look-back procedure must be established so the fractionator can be informed.

5.10 Appropriate clinical use

Good diagnostic facilities for bleeding disorders and sufficient knowledge among the medical community should ensure that blood-derived products obtained through contract fractionation are used effectively and efficiently.

5.11 Financial considerations

The following checklist contains budget items that should be taken into consideration for the collection of plasma for contract fractionation. Some cost-sharing with blood cellular components is possible.

Budget Items for Contract Fractionation

- Testing material
- Laboratory disposables: syringes, needles, bags for blood collection
- Equipment for the extraction of plasma
- Freezing storage facilities both at blood collection centres and a central warehouse
- Transportation costs from blood collection centres to central storage facilities
- Transportation costs from storage to fractionation plant (and back)
- Travel expenses for regular inspections and visits to fractionation plant
- Laboratory and quality assurance staff
- Fractionation fee
- Registration costs
- Marketing costs of products within and outside the country of origin, depending on the contract
- Highly qualified staff to supervise the whole operation
- If needed, investment costs related to the increase in blood collection (new blood collection centres with equipment and personnel)

In the most likely scenario, there will be insufficient recovered plasma to meet the requirements. Therefore, plasmapheresis will be necessary and the following costs must be added:

- Capital cost of plasmapheresis equipment
- Ongoing cost of plasmapheresis

6. Selection of the Plasma Fractionator

When selecting a fractionator, health officials must ensure that the fractionator meets the following criteria.

6.1 Good manufacturing practice

The fractionator must be licensed in its country and regularly subjected to inspections by the relevant NRA to establish that its full operation adheres to GMP. The contracting blood collection organization should have access to inspection reports.

Use of GMP ensures compliance with established best production practices and provides a guarantee of quality operation in terms of production criteria and quality assurance. Adherence to GMP also means extensive, detailed documentation is kept regarding the manufacture of every batch of product, traceability, and the correct operation of the fractionation facility. The fractionator should be asked to provide a complete review of its GMP procedures.

6.2 Quality control

The quality control mechanism in place is of utmost importance. The fractionator should be asked to provide details on the mechanisms used at its facility.

6.3 Custom-built premises

A modern fractionation facility must be housed in custom-built, licensed premises offering a clear separation of those products that are viral-inactivated from those that are not. If the facility is designed properly, the basic elements of GMP will already have been incorporated into the design, including air-handling systems, air pressure differentials between areas, limited access, and state-of-the-art viral inactivation and removal methods.

6.4 Batch sizes and batch segregation

Some countries have limited storage capacity for frozen plasma and must therefore send small batches to the fractionator. These small batches may be stored by the fractionator and pooled together for fractionation when a sufficient volume of plasma is reached, as would be specified in the contractual agreement.

The minimum batch size of donations recommended by WHO (250 L of plasma = 1,000 blood donations) guarantees that there are enough donors to ensure a convenient mixture of antibodies in the preparation derived from the pool. As mentioned previously, actual industrial batch sizes are bigger.

The capacity for the fractionator to guarantee segregation of plasmas from different origins may be a choice criterion.

6.5 Product portfolio and specification

The capacity of the fractionator to provide products meeting local needs should be considered, for instance the capability to manufacture 250 I.U. vials for factor VIII and factor IX concentrates, which are still often used in the developing world. Other criteria include shelf-life and storage conditions (specifically temperature).

6.6 History

An additional way to evaluate a fractionator is to look at its history of avoiding viral transmission, its capacity to introduce new products, and its products under development. A list of the countries where the products are currently licensed and for how long also provides helpful information.

7. Contractual Agreement

The contractual agreement between the fractionator and the responsible local entity should be regarded as a pharmaceutical manufacture contract.

Various important technical aspects, in addition to financial and legal considerations, should be covered and need to be in compliance with the regulatory documents.

7.1 Products and manufacturing method

The contract should clearly specify:

- The list of products to be manufactured;
- The manufacturing methods that will be used, including the viral inactivation treatments, in compliance with the respective product registration files;
- The full specifications of the products (including purity and potency);

- Product labeling and packaging;
- Requirements or not for batch release by regulatory authorities;
- Minimum and maximum batch size for the starting plasma and the end-products;
- Average minimum guaranteed yield of the products per litre of plasma received annually in each contracted year;
- Quantities of product to be manufactured yearly;
- Processing time to delivery;
- Delivery terms (frequency, transportation means and conditions);
- When appropriate, a statement that plasma and product processes will be segregated from other origins;
- When appropriate, an indication on how by-products, (or intermediates) or excess products from the contract fractionation will be handled (sale, destruction);
- Place of fractionation (in case the manufacturer has several plants);
- A declaration of compliance with GMP by the fractionator.

7.2 Raw material

The quality criteria of the plasma raw material should be defined and guaranteed, in particular with regards to traceability, viral screening test requirements, quantity of protein or factor VIII, storage conditions, and transportation.

The conditions for delivery should also be stated (e.g. batch size per shipment frequency, documentation).

The contract should state whether additional screening tests (such as NAT) must be performed by the fractionator.

7.3 Quality assurance and documentation

It is important that the contract specify the following:

- Documentation needed from the plasma supplier and from the fractionator;
- Batch record system;
- Traceability system;
- Archiving system for plasma, intermediates, and final products;
- Names and contacts of responsible persons on both sides.

7.4 Financial aspects

A fractionation fee can be expressed as a cost to be paid per litre of plasma fractionated (with a certain amount of products to be manufactured), or as a cost per gram or I.U. of product returned. The cost will be a function of the number of products made, the recovery achieved, and the batch size (which all influence the productivity of the fractionation).

The cost to be paid is itself influenced by three possible scenarios:

- All plasma products are returned to the country of origin ;
- Some products, such as albumin or immunoglobulins, are retained and sold by the fractionator under its own name, offseting part or all of the fractionation fee. This type of financing is used when only some products, such as coagulation factors, are needed by the country of origin;
- A certain percentage of all products is kept by the fractionator to offset part or all of the fractionation fee. If the agreed yield is, for example, 165 units of factor VIII per litre of plasma and the fractionator gets 200 units per litre, it can sell the extra 35 units for profit.

These last two possibilities imply that the fractionator's product licenses (or plasma master file) cover the use of this starting plasma material.

7.5 Other aspects

Other aspects to be covered include:

- Reciprocal inspection rights
- Liability issues
- Product pharmacovigilance
- Marketing

8. Contract Fractionation vs. Building a Fractionation Facility

A decision to choose contract fractionation vs. construction of a local plant may involve consideration of the following factors:

- Fractionation plants require a large capital expenditure – at least US $50-100 million in construction cost (engineering, building and equipment) for a plant of minimum capacity (100,000-300,000 L per year).

- In some situations the private sector may be interested in investing in such a facility, provided an agreement ensures access to local plasma over a reasonable period of time (e.g. 10-20 years).
- Fractionation plants are high-technology facilities which require highly skilled workers and constant upgrading to keep up with changing safety requirements.
- Fractionation plants require an adequate volume of plasma – a minimum of 100,000 L per year – to achieve cost efficiency. Officials must consider whether the existing national blood transfusion service provides both the volume and the quality of plasma required for fractionation.
- The production costs of a national fractionation plant should be competitive with the cost of products that could be obtained through contract fractionation or purchased on the international market.

Contract fractionation is the solution chosen at different times by several countries, including Brazil, Canada, Hong Kong, Greece, Indonesia, Ireland, Luxembourg, Malaysia, Morocco, New Zealand, Norway, Poland, Singapore, Taiwan, and Tunisia. In some of these countries, health officials considered that their population base and financial situation did not justify the investment in a fractionation plant. In a few of those countries, the contract fractionation phase has been seen as a first, ramp-up step prior to considering the construction of a local plant.

9. Plasma Fractionators

The following are lists of industrial and non-profit plasma fractionators. The number of fractionators has been dramatically reduced over the last few years due to consolidation. Not all of these fractionators are involved in contract fractionation activities.

9.1 Industrial Plasma Fractionators

The table below provides yearly fractionation capacities in million litres of plasma for plasma fractionators currently in operation. Restructuring in the industry is fast and may change the mentioned figures.

Company	Plant Location	Fractionation Capacity Range (in million litres)
Baxter	U.S.A., Austria, Belgium	4 to 6
CSL	Australia, U.S.A., Germany, Switzerland, Austria, Spain	3 to 5
Talecris	U.S.A., Italy	2 to 4
Instituto Grifols SA	Spain, U.S.A.	2 to 4
Octapharma AG	Austria, France, Sweden	1 to 2
Biotest Pharma GmbH	Germany, U.S.A.	0.5 to 1.2
RAAS	China	0.3 to 0.5
Korean Green Cross	Korea	0.3
Kaketsuken	Japan	0.3

9.2 Main government and non-profit organization plasma fractionators

The plasma fractionators owned by governments or not-for-profit organizations are listed in the table below.

Company	Plant location
Bio Product Laboratory (BPL)	England
German Red Cross (DRK)	Germany
Laboratoire Français du Fractionnement et des Biotechnologies (LFB)	France
Magen david Adom (Blue Shield of David, Israeli Red Cross)	Israël
Natal BioProducts Institute	South Africa
Japanese Red Cross Fractionation Center (JRC)	Japan
Sanquin	Holland, Belgium

Glossary of Terms

albumin – one of the plasma products used for transfusion/volume replacement when large volumes of blood have been lost.

alpha 1 antitrypsin – serine protease inhibitor that inactivates an enzyme responsible for the development of emphysema.

batch – plasma from various donors that is combined and treated together at the industrial level.

coagulation factors – blood derivative products. The main coagulation factors (factors VIII and IX) are used to treat hemophilia.

contract fractionation – an agreement made by contract between a plasma collection organization or other entity of one country and a fractionator, usually in another country. The country of origin collects plasma and sends it to the fractionator, who processes it and returns all or part of the resulting products to the country of origin, according to contractual terms.

fibrin sealant - a type of surgical glue that is made from human blood-clotting proteins

fractionation – separation and processing of human blood plasma into a range of products for therapeutic use. A fractionation plant is a facility that carries out fractionation. A fractionator is the company or organization that owns and administers the plant.

good manufacturing practice (GMP) –that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use, and as required by the marketing authorization or product specification.

immunoglobulins – blood components responsible for immune function (defending the body against infection or playing a role in modulating body's immunological mechanisms). This component can be separated out during fractionation.

inhibitors (coagulation factor inhibitor) – antibodies that destroy all or part of injected clotting factor.

plasmapheresis – procedure in which whole blood is removed from the donor, the plasma is separated from the cellular elements and at least the red blood cells are returned to the donor This method allows a donor to donate a larger volume (up to 800 ml) of plasma more frequently than through the donation of whole blood (about 200-220 ml of plasma).

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