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**GUIDELINES FOR BLOOD DERIVED PRODUCTS**

 [**Ministry of National Health Services, Regulations and Coordination**](http://www.nhsrc.gov.pk/) **ISLAMABAD**

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# Introduction:

This is the first edition of these guidelines, in Pakistan there is no such document on components of Blood or plasma. It is a critical component of a healthcare system, and its importance cannot be denied. It is estimated that millions of lives are saved annually through blood transfusions; however, huge volume of Plasma is wasted in Pakistan. With a rapid population increase in Pakistan, the demand for blood transfusions and its products is also rising, mainly due to the increased number of inherited diseases, surgical procedures, accidents, and chronic illnesses.

The guidelines provide comprehensive guidance for blood related products in Pakistan. The document aims to improve access to safe and quality blood transfusion services and universal access to blood products while protecting individuals’ health and human rights and provides guidance on the entirety of blood transfusion, including the collection, processing, and storage of blood and the distribution and use of blood products. Guidance was also provided on quality management, including developing quality standards, monitoring and evaluating blood transfusion services, and accreditation of blood banks. It also addresses the ethical and legal aspects of blood transfusion, including the rights of patients, donors, and healthcare providers.

# Application:

This document is applicable to the entity/firms who intend to apply for registration/Marketing Authorization of blood derived products i.e., Immunoglobulins, Albumin, Coagulation Factors, Protease inhibitors and others. It also applicable to industries who intend to obtain plasma from donors, export to fractionating plant and importing the finished product with traceability of the exported plasma subject to NoC from Ministry of NHSR&C.

# Scope:

The scope of this guide is upstream process of starting material of blood derived products, its logistics handling and importing in the form of finished product for human use.

The scope does not cover blood or blood components. Furthermore, it does not cover medicinal products prepared on a small scale for individual patients in accordance with a medical prescription, although many parts contained in this document may be pertinent.

# Background:

Section 7 (c) (ix) of DRAP Act 2012, mandated the systematic implementation of internationally recognized standards of World Health Organization, International Conference on Harmonization (ICH), and Food and Drug Administration guidelines etc.

**These guidelines conform and shall be read in consistence to DRAP Act, 2012 and Drugs Act 1976 and Rules framed there under.**

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# General Consideration:

The setting up of an organization for the collection and fractionation of human blood and blood components calls for a great deal of expertise and considerable investment. A logical developmental sequence for a comprehensive organization starts with the collection and distribution of whole blood, progressing later to the separation of whole blood into components and then the fractionation of plasma pools.

Blood can harbor several different viruses, and the use of medicinal products derived from human blood has led to transmission of viruses such as HBV, HCV and HIV. The risk of virus transmission by blood and blood products can be diminished by the testing of all individual donations.

The transport of source materials from blood collecting centers and hospitals to fractionation facilities requires special consideration. Refrigeration at the temperature range appropriate for the product must be efficient and reliable and proved to be so by monitoring. Thermal insulation must provide an adequate safeguard against a temporary failure of refrigeration. Containers of liquid source material should be filled so as to minimize frothing due to shaking. Because of the potentially infective nature of these biological materials, suitable protection should be provided against breakage, spillage and leakage of containers.

# Definitions:

The following definitions are intended for use in this document and are not necessarily valid for other purposes.

***Blood collection:*** a procedure whereby a single donation of blood is collected in an anticoagulant and/or stabilizing solution.

***Processing:*** any procedure that takes place after the blood is collected

***Plasmapheresis,*** apheresis; procedures whereby whole blood is separated by physical means into components and one or more of them returned to the donor

***Plasmapheresis Facility: A physical center to conduct apheresis process on the plasma donors***

***Fractionation:*** A (large-scale) process by which plasma is separated into individual protein fractions, that are further purified for medicinal use (variously referred to as plasma derivatives, fractionated plasma products or plasma derived medicinal products). The term fractionation is used to describe a sequence of processes, including; plasma protein separation steps (typically precipitation and/or chromatography), purification steps (typically ion exchange or affinity chromatography) and one or more steps for the inactivation or removal of blood-borne infectious agents (most specifically viruses and, possibly, prions).

***Fractionator:*** A company or an organization performing plasma fractionation to manufacture plasma-derived medicinal products.

***Closed blood-collection and processing system:*** a system for collecting and processing blood in containers that have been connected together by the manufacturer before sterilization, so that there is no possibility of bacterial or viral contamination from outside after collection of blood from the donor.

***Donor:*** a person who gives blood and fulfills all criteria (AABB / WHO Criteria).

***Whole blood*** (sometimes referred to as "blood"): blood collected in an anticoagulant solution with or without the addition of nutrients such as glucose or adenine. Whole blood is collected in units of 450 ml.

***Blood component:*** any part of blood separated from the rest by means of physical procedures.

***Plasma:*** the liquid portion remaining after separation of the cellular elements from blood collected in a receptacle containing an anticoagulant or separated by continuous filtration or centrifugation of anticoagulated blood in an apheresis procedure.

***Plasma, fresh-frozen:*** a plasma separated within 4-6 hrsof donation, frozen rapidly and stored below -20 0C to -80 C.

***Plasma, platelet-rich***: a plasma containing at least 70% of the platelets of the original whole blood.

***Plasma, freeze-dried:*** any one of the above forms of plasma that has been freeze-dried for preservation.

***Plasma,*** ***recovered:*** plasma recovered from a whole blood donation.

***Cryoprecipitated factor VIII***: a preparation containing factor VIII that is obtained from single unit (or small pools) of plasma derived either from whole blood or by plasmapheresis, by means of a process involving freezing, thawing and precipitation.

***Serum:*** the liquid part of coagulated blood or plasma.

***Red cells:*** whole blood from which most of the plasma has been removed and having an erythrocyte volume fraction greater than 0.7.

***Red cells suspended in additive solution***: red cells to which a preservative solution, for example containing adenine, glucose and mannitol, is added to permit storage for longer periods; the resulting suspension has an erythrocyte volume fraction of approximately 0.6-0.7.

***Red Cell Washed***: Red cells from which most of the plasma has been removed by one or more stages of washing with an isotonic solution.

***Red cells, leukocyte-depleted*** a unit of a red-cell preparation containing fewer than 1.2 X 109 log leukocytes.

***Red cells, leukocyte-poor***: a unit of a red-cell preparation containing fewer than 5 X 106 leukocytes

***Red cells, frozen***: red cells that have been stored continuously at -65 0C or below, and to which a cryoprotective agent such as glycerol has been added before freezing.

***Red cells, deglycerolized***: frozen red cells that have been thawed and from which glycerol has been removed by washing.

***Platelets:*** Platelets obtained either by separation of whole blood, buffy coat or platelet-rich plasma or by apheresis and suspended in a small volume of plasma from the same donation.

***Leukocytes:*** leukocytes obtained either by the separation of whole blood or by apheresis and suspended in a small volume of plasma from the same donation.

***Bulk material:*** plasma, powder, paste or liquid material prepared by the fractionation of pooled plasma.

***Final bulk:*** a sterile solution prepared from bulk material and bearing the corresponding batch number. It is used to fill the final containers

***Plasma master file:*** document which provides all relevant detailed information on the characteristics of the entire human plasma used by a fractionator as starting material and/or raw material for the manufacture of sub-intermediate or intermediate plasma fractions, constituents of the excipient and active substance(s), which are part of a medicinal product.

# REQUIREMENTS FOR THE COLLECTION OF SOURCE MATERIALS

## **Premises**

The premises shall be of suitable size, construction and location to facilitate their proper operation, cleaning and maintenance in accordance with accepted rules of hygiene. They shall comply with the requirements of Good Manufacturing Practices for Pharmaceutical and Biological Products and in addition provide adequate space, Lighting and ventilation for the following activities where applicable:

* + 1. The medical examination of individuals in private to determine their fitness as donors of blood and/or blood components and to provide an opportunity for the confidential self-exclusion of unsuitable potential donors.
		2. The withdrawal of blood from donors and, where applicable, the re-infusion of blood components with minimum risk of contamination and errors.
		3. The care of donors, including the treatment of those who suffer adverse reactions.
1. The storage of whole blood and blood components in quarantine pending completion of processing and testing.
2. The laboratory testing of blood and blood components.
3. The processing and distribution of whole blood and blood components in a manner that prevents contamination and loss of potency.
4. The performance of all steps in apheresis procedures, if applicable.
5. The performance of labelling, packaging and other finishing operations in a manner that prevents errors.
6. The storage of equipment.
7. The separate storage of quarantined and finished products.
8. The documentation, recording and storage of data on the donor, the donated blood and the ultimate recipient.
9. Mobile teams can be used for the collection of blood. Although the premises used by such teams may not comply with the more stringent requirements for centers built specially for the purpose, they must be adequate to ensure the safety of the donor, the collected blood or blood components and the staff participating in blood collection. The safety of the subsequent users of the premises should also not be forgotten.

## **Equipment**

The equipment used in the collection, processing, storage and distribution of blood and blood components shall be calibrated, tested and validated before initial use, and shall be kept clean and maintained and checked regularly. The requirements of Good Manufacturing Practices for Pharmaceutical and Biological Products shall apply in every particular.

## **Personnel**

An organization for the collection of blood or blood components shall be under the direction of a designated and appropriately qualified person who shall be responsible for ensuring that all operations are carried out properly and competently. The director shall have adequate knowledge and experience of the scientific and medical principles involved in the procurement of blood and. if applicable, the separation of blood components and the collection of such components by apheresis.

The director shall be responsible for ensuring that employees are adequately trained and acquire practical experience and that they are aware of the application of accepted good practice to their respective functions.

The persons responsible for the collection of the blood and blood components shall be supervised by licensed Medical Doctor who shall be responsible for all medical decisions, for review of the procedure’s manual and for the quality-control program, including techniques, equipment, procedures and staff.

The personnel responsible for the processing, storage, distribution and quality control of blood, blood components and plasma shall be adequate in number and each member of the personnel shall have a suitable educational background and training or experience that will ensure competent performance of assigned functions so that the final product has the required safety, purity, potency and efficacy.

## **Donors**

Starting material for fractionation is plasma which can be obtained either from whole blood donations or by plasmapheresis. Selection of donors and testing of donations and plasma pools, are important factors in the safety of plasma-derived medicinal products:

## **Donor Selection:**

In selecting individuals for blood donation, it is most important to determine whether the person is in good health, in order to protect the donor against damage to his or her own health and to protect the recipient against exposure to diseases or to medicinal products from the blood or blood products. It should be recognized that the donor selection process contributes significantly to the safety of blood products derived from large plasma pools. The following provisions apply to donations of blood or blood components not intended for autologous use:

The health of a donor shall be determined by a licensed physician, and the donor shall be free from any disease transmissible by blood transfusion so far as can be determined by history-taking and physical examination and specific laboratory test. Donors shall be healthy persons of either sex between the ages of 18 and 65 years (AABB/ WHO).

A donor should be considered for plasmapheresis only where the procedures involved result in products or services shown to serve accepted medical purposes, including prophylaxis, therapy and diagnosis, as verified by valid scientific evidence. All donors should be certified as acceptable, at the time of each plasmapheresis procedure, by a registered physician or by trained personnel under the direct supervision of the concerned physician.

## **Donor Exclusion:**

Persons in the following categories shall be excluded from acting as donors:

1. Those with clinical or laboratory evidence of infectious disease, e.g. infection with hepatitis viruses, HIV-1 or HIV-2; Syphilis
2. Past or present intravenous drug abusers.
3. Situations or conditions where sexually transmitted diseases are more vulnerable.
4. Those with haemophilia or other clotting-factor defects who have received clotting-factor preparations.
5. Persons who have received blood transfusion should be excluded from acting as donors for at least one year.
6. Donors shall not have undergone tooth extraction or other minor surgery during a period of 72h before donation.
7. Pregnant women shall be excluded from blood donation. In general, mothers shall also be excluded during lactation and for at least six months (one year) after full-term delivery.
8. Before each donation, a medical history by qualified person (medical doctor) shall be taken so as to ensure that the donor is in normal health and has not suffered, or is not suffering, from any serious illness. A donor who appears to be under the influence of any drug including alcohol or who does not appear to be providing reliable answers to medical history questions shall not be accepted.
9. Symptom-free donors who have recently been immunized may be accepted with the following exceptions:
10. Those receiving attenuated vaccines for measles, mumps, yellow fever or poliomyelitis shall be excluded until two weeks after the last immunization or injection.
11. Those receiving attenuated rubella (German measles) vaccine shall be excluded until four weeks after the last injection
12. Those receiving rabies vaccine for post-exposure treatment shall be excluded until one year after the last injection.
13. Those receiving passive immunization with animal serum products shall be excluded until four weeks after the last injection.
14. Those receiving hepatitis B vaccine need not be excluded unless the vaccine is being given because of exposure to a specific risk, in which case the donor shall be disqualified for at least 12 months after the last such exposure. If hepatitis B immunoglobulin has been administered, the period of deferral shall be at least 12 months because disease onset may be delayed.
15. Blood and plasma shall be tested for the presence of HBsAg, anti-HIV, anti-HCV, syphilis by Elisa / CLIA or NAAT and malaria by ICT. Anyone whose blood has been shown to be reactive for infectious disease markers by approved screening tests shall be excluded as a donor.

## **Donors for Plasmapheresis:**

All phases of apheresis, including, physical examination, laboratory testing, explaining to donors what is involved in the process and obtaining their informed consent, should be performed under the direct supervision of a licensed physician or by trained personnel reporting to such a physician.

First-time plasma donors

When prospective plasma donors present themselves to a center for the first time, initial screening shall begin only after the procedure of plasmapheresis has been explained and the donor has given consent.

The following information shall be permanently recorded:

1. Personal information and identification. If the donor is to participate in an ongoing program, an effective means of identification is especially important. The use of identity numbers, photographs or other equally effective measures should be considered.
2. A preliminary medical history as required for blood donors, covering infectious diseases and the donor's general state of health.

The following tests shall be performed for first time donors to qualify for the plasma donor:

1. Measurement of hemoglobin concentration or erythrocyte volume fraction.
2. Determination of total serum protein concentration, which shall be at least 60 g/l.
3. An approved test for HBsAg, which shall be negative.
4. An approved test for anti-HIV (1&2), which shall be negative.
5. An approved test for anti-HCV, which shall be negative.
6. An approved test for syphilis, which shall be negative.
7. An approved test for malaria, which shall be negative.

Initially reactive donations should be retested in duplicate by the same assay. A sample of the donation should be evaluated by a confirmatory test and if confirmation is positive a system should exist to notify and counsel the donor.

Donors who have undergone plasmapheresis previously in the same program:

For donors who have already taken part in a plasmapheresis program:

1. The receptionist shall note the date of the last donation (at least two days must have elapsed since that time). No more than two donations shall be permitted within a seven-day period.
2. The medical history and weight of the donor shall be recorded; blood pressure, temperature, pulse rate and hemoglobin concentration shall be measured by trained personnel. On the day of each donation, in addition to meeting the general requirements for donors, plasma donors shall be shown to have a total serum protein concentration of not less than 60 g/l.

Whenever the result of a laboratory test is found to be outside the established normal limits or a donor exhibits any remarkable abnormalities of history or on physical examination, the donor shall be excluded from the program.

## **Collection of Plasma**

Plasma is prepared either from whole blood or from plasma collected by apheresis and is frozen within a defined period of time to a temperature that should adequately maintain the labile coagulation factors in a functional state, consistent with the intended use of the plasma. In particular, Factor VIII content is critical both as a quality indicator and to assure the efficacy of cryoprecipitate.

If plasma is separated from a unit of whole blood that is refrigerated to 4°C, centrifugation should preferably take place within eight (4-6) hours of collection.

If the whole blood unit is rapidly cooled to 20–24°C and maintained at this constant temperature after collection, separation can take place within 18– 20 hours because such conditions have been found to protect Factor VIII.

If plasma is collected by apheresis, the freezing process should begin as soon as possible, and ideally not later than six hours after the completion of the apheresis process.

The freezing process should be validated and should take place in a system that will allow complete freezing to a predefined core temperature in a predefined time.

Product stability is dependent on the storage temperature. Storage temperature and shelf-life depend on the intended use of the product. For long-term storage (more than one year) the optimal storage temperature is minus 20°C or colder.

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent. At a minimum, the following critical parameters should be checked during the quality control assays:

* Visual changes.
* Volume
* Factor VIII activity (especially if plasma is used to treat Factor VIII deficiencies);
* Residual leukocytes, if leukocyte reduction is performed.
* Leakage.

## **Apheresis Procedures**

The skin of the donor at the site of venipuncture shall be prepared by a method that has been shown to give reasonable assurance that the blood collected will be sterile.

With apheresis procedures, care shall be taken to ensure that the maximum volume of erythrocytes is returned to the donor by intravenous infusion. If the red cells cannot be returned to the donor, no further collection should be made until the donor has been re-evaluated. Several checks shall be made to ensure that donors receive their own erythrocytes, including identification of the containers of erythrocytes by donors before reinfusion. Haemolytic transfusion reactions are avoidable since they are caused by the accidental infusion of incompatible erythrocytes. Personnel involved in reinfusion procedures should be adequately trained to prevent them. The signs and symptoms are hypotension: shortness of breath, stomach and/or flank- pain, apprehension, cyanosis and haemoglobinuria.

If a haemolytic transfusion reaction occurs, the infusion of cells to all donors at the center concerned should be discontinued until the identity of all containers of erythrocytes has been checked. Automated plasmapheresis is preferred to manual plasmapheresis because of its greater safety.

## **Summary of Minimum General Requirements for Apheresis:**

***Equipment:*** This must be electrically safe and non-destructive for blood elements; disposable tubing must be used wherever there is blood contact. In addition, equipment must be accessible to detailed inspection and servicing and its decommissioning should not significantly interrupt the program. It should also be provided with suitable automatic alarms.

***Procedure:*** This must be non-destructive for blood elements and aseptic; there must be adequate safeguards against air embolism.

***Disposables:*** These must be pyrogen-free, sterile and biocompatible (e.g., there must be no activation of enzyme systems).

***Containers:*** Containers shall be uncolored and translucent, and the labelling shall be placed in such a position as to allow visual inspection of the contents. They shall be sterilized and hermetically sealed by means of suitable closures so that contamination of the contents is prevented. The container material shall not interact adversely with the contents under the prescribed conditions of storage and use.

**Identification of samples**

Each container of blood, blood components and pilot and laboratory samples shall be identified by a unique number or symbol so that it can be traced back to the donor and from the donor to the recipient. The identity of each donor shall be established both when donor fitness is determined and at the time of blood collection.

When blood-derived materials are transferred to a fractionation plant, the following details shall be provided by the supplier:

* 1. name and address of collecting center
	2. type of material
	3. donor identification
	4. date of collection
	5. results of mandatory tests
	6. conditions of storage
	7. other details required by the fractionator
	8. name and signature of responsible person with date
	9. Weight (the standard collected plasma volume is 450ml to 880ml per donation)

## **Laboratory Testing of Collected Plasma**

Screening tests for infectious disease markers:

The following tests, which are considered mandatory by all regulatory agencies, are relevant to the preparation of blood components and should be performed on each individual blood donation:

1. an approved test for Hepatitis B surface antigen (HBsAg);
2. an approved test for anti-HIV1/HIV2;
3. an approved test for anti-HCV.
4. an approved test for syphilis.
5. an approved test for malaria.

All four tests have to be negative. Initially reactive donations should be retested in duplicate by the same / advanced assay. Products from a reactive donation should not be used for therapeutic applications and should normally be destroyed.

Storage and Transport

The plasma is prepared by a method that removes cells and cell debris as completely as possible. Whether prepared from whole blood or by plasmapheresis, the plasma is separated from the cells by a method designed to prevent the introduction of microorganisms. No antibacterial or antifungal agent is added to the plasma. The containers comply with the requirements for glass containers or for plastic containers for blood and blood products. The containers are closed so as to prevent the possibility of contamination. If two or more units are pooled prior to freezing, the operation is carried out using sterile connecting devices or under aseptic conditions and using containers that have not previously been used.

Plasma, intended for the recovery of proteins, is frozen within 24 hours of collection by cooling rapidly in conditions validated to ensure that a temperature of – 20 ᵒC or below is attained at the core of each plasma unit within 12 hours of placing in the freezing apparatus.

Frozen plasma is stored and transported in conditions designed to maintain the temperature at or below – 20 ᵒC. For accidental reasons, the storage temperature may rise above – 20 ᵒC on one or more occasions during storage and transport but the plasma is nevertheless considered suitable for fractionation if all the following conditions fulfilled:

* The total period during which the temperature exceeds – 20 ᵒC does not exceed 72 h;
* The temperature does not exceed – 15 ᵒC on more than one occasion;
* The temperature at no time exceeds – 5 ᵒC.

The recommendations for cold chain maintenance, as mentioned for plasma storage, should also apply during transportation of plasma. The arrangements for temperature control and monitoring during shipping should be clearly defined and documented. The requirements for number and location of temperature logging devices during shipping should be based on a documented assessment of risk throughout the process. The temperature to be maintained during transportation should be defined by the fractionator in accordance with relevant regulations.

# Compliance with plasma fractionator requirements

Any plasma collected and prepared for fractionation should meet the plasma product manufacturer requirements as per approval of Ministry of NHSR&C. As the specifications of plasma for fractionation are part of the marketing authorization granted by the national regulatory authority for a specific plasma derivative. In addition, to the regulatory criteria related to donor selection and screening of donations, the quality specifications agreed upon with the fractionator may encompass:

* + - 1. compliance with WHO standards during production and control;
			2. residual level of blood cells (platelets, leukocytes) that should be below a certain level that may vary depending upon the requirements of different countries or fractionators;
			3. protein content possibly including a minimal mean level of Factor VIII coagulation activity if this product is manufactured;
			4. guarantee of an appropriate ratio of plasma: anticoagulant solution and evidence of appropriate mixing with the anticoagulant during the collection process (for instance, clots should be absent);
			5. acceptable maximum titer of ABO blood group antibodies (risks of haemolytic reactions due to the presence of ABO antibodies, or antibodies to other blood group systems, in intravenous IgG and low purity factor VIII preparations have been described (68)). The European pharmacopoeia requires an ABO titer of less than 1:64 for the release of plasma products for intravenous use.
			6. maximum haemoglobin content;
			7. absence of haemolysis;
			8. colour;
			9. absence of opalescence (due to lipids);
			10. citrate (anticoagulant) range content (usually between 15 and 25 mM); and
			11. minimum titer of a specific antibody when the donation is used for the production of hyperimmune IgG such as anti-Rho, anti-HBs, anti-tetanus or anti-rabies.

# Release of plasma for fractionation

Each blood establishment should be able to demonstrate that each unit of plasma has been formally approved for release by an authorized person assisted by validated information technology (IT)-systems. The specifications for release of plasma for fractionation should be defined, validated, documented and approved by quality assurance and the fractionator.

# Contract plasma fractionation program:

The fractionation of plasma requires specialized facilities, with provision for large-scale protein separation, purification, virus inactivation and formulation, as well as for aseptic finishing and freeze-drying. The preparation of plasma-derived products should be governed by the same regulatory considerations that are applied to medicines. Manufacturers are required to obtain manufacturing licenses which should cover the method of preparation and product characteristics. To obtain a license, it is necessary to demonstrate adherence to defined criteria by WHO. Considerable technological, pharmaceutical and scientific expertise is required to meet these demands. Since key utilities (such as heating, ventilation and air-conditioning (HVAC), refrigeration and water for injection) should be maintained operational even when the facility is not fractionating plasma, the investment in and running costs of fractionation are substantial. The economic viability of a fractionation facility will be determined by:

* + - 1. the cost of the plasma for fractionation (in particular cost-allocation of the whole blood collection system on plasma versus labile components);
			2. the operating capacity of the facility; and
			3. plasma availability and product demand to allow the facility to operate continuously at near to maximum capacity.

This policy entails the export of plasma till the availability of facility / plant for plasma farming in Pakistan. The purpose of this policy is to provide guidelines to the potential contract to be signed between the plasma supplier and the fractionator. These may include:

* + - 1. commercial and quality agreements defining the responsibilities of both parties (the contract giver and the contract acceptor);
			2. clearly defined requirements for plasma quality (including the arrangements for donor selection, testing and traceability);
			3. provision for audit of the plasma collection center (by the fractionator) and inspection by an appropriate regulatory body;
			4. formal approval of the contract plasma fractionation activities by the regulatory authority of the fractionator;
			5. a contractual commitment to supply agreed quantities of plasma. The annual minimal volume is dependent upon the fractionator’s overall free capacity and specific aspects of production such as plasma pool and product batch size;
			6. agreement on the arrangements for storage and shipment of plasma, with defined provisions for monitoring and control (typically transport by sea, at –20 °C or below);
			7. agreement on the range of products to be manufactured; and
			8. agreement on specific aspects of plasma processing (including batch size, possible requirements for segregation of processing, agreed use or destruction of excess intermediates, expected yield and toll fees).

Plasma products made from local plasma need to receive a specific registration, even if the same products made from foreign plasma are already licensed in the country of origin.

The regulatory authorities of the country where the plasma is collected may require inspection of the fractionation center. Table 1 summarizes the responsibilities and roles of each party.

# Promoting Local Plasma Industry:

With the objective of promoting local plasma industry, the Ministry of NHSR&C may recommend, and the Federal Government may grant additional incentives and exemptions to including but not limited to subsidies, benefits, exemptions and protections after completion of all codal formalities and endorsement of relevant authorities. Incentives, benefits and protections shall be additional to all incentives, benefits and protections, which may be applicable to Plasmapheresis Facilities and Fractionators under generally applicable legislation and international agreements of Pakistan. These incentives shall not be withdrawn or modified or altered prematurely and retrospectively and any change therein shall be to the advantage of the Plasmapheresis Facilities and Fractionator and not otherwise. The following incentives (all/any) may be the provided to Plasmapheresis Facilities and Fractionators after completion of all codal formalities as stated above;

1. Exemption from all taxes under the Income Tax Ordinance, 2001 including tax on profits and gains, income tax, turnover tax, withholding tax, capital gains tax, income tax on dividend income and withholding tax on dividend
2. Exemption from sales tax under the Sales Tax Act, 1990
3. Exemption from Customs Duty under the Customs Act 1969 on the import in Pakistan of all Capital Goods including but not limited to materials plant, machinery, hardware, equipment and software, devices, instruments, accessories, attachments, building materials, materials and any other equipment required to perform functions, whether or not manufactured locally, for use in Plasmapheresis Facilities and Fractionation.
4. Exemption from property tax
5. Exemption on dividend income and capital gains of any venture capital fund (whether local or foreign) derived from investments in the plasma centers; and
6. permission for opening and maintaining of foreign currency accounts, availability of foreign exchange, full convertibility to foreign currency and repatriation and free transfer of foreign currency to meet the requirements of investors, lenders, contractors, operators, consultants, insurers, re-insurers, vendors and advisors in relation to any compensation amounts, loan repayments, equity and return on equity, profits, works, goods and services in accordance with the foreign exchange regulations of the State Bank of Pakistan for zones.

**Table-1**

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# Appendix-1 Plasma products and clinical applications

Adapted from: Ala, F, Burnouf T, El-Nageh M. *Plasma fractionation programmes for developing economies. Technical aspects and organizational requirements.* Cairo, WHO Regional Publications, 1999 (Eastern Mediterranean Series).

|  |  |
| --- | --- |
| **Products** | **Main indications** |
| **Albumin** |   |
| Human serum albumin | Volume replacement |
| **Blood coagulation factors** |   |
| Factor VIII | Haemophilia A |
| Prothrombin complex | Complex liver diseases; warfarin or coumarin derivatives reversal |
| Factor IX | Haemophilia B |
| Factor VII | Factor VII deficiency |
| Von Willebrand factor | Von Willebrand disease  |
| Factor XI | Haemophilia C (factor XI deficiency) |
| Fibrinogen | Fibrinogen deficiency |
| Factor XIII | Factor XIII deficiency |
| Activated PCC | Haemophilia with anti-factor VIII (or factor IX) inhibitors |
| **Protease inhibitors** |   |
| Antithrombin | Antithrombin deficiency |
| Alpha 1 antitrypsin | Congenital deficiency of alpha 1 antitrypsin with clinically demonstrable panacinar emphysema |
| C1-inhibitor | Hereditary angioedema |
| **Anticoagulants** |   |
| Protein C | Protein C deficiency |
| Fibrin sealant (fibrin glue) | Topical haemostatic/healing/sealing agent (surgical adjunct) |
| **Intramuscular immunoglobulins (IMIG)** |   |
| Normal (polyvalent) | Prevention of hepatitis A (also rubella, and other specific infections) |
| Hepatitis B | Prevention of hepatitis B |
| Tetanus | Treatment or prevention of tetanus infection |
| Anti-Rho (D) | Prevention of haemolytic disease of the newborn |
| Rabies | Prevention of rabies infection |
| Varicella/zoster | Prevention of chickenpox infection |
| **Intravenous immunoglobulins (IVIG)** |   |
| Normal (polyvalent) | Replacement therapy in immune deficiency states; |
| Cytomegalovirus (CMV) | Prevention of CMV infection (e.g., after bone marrow transplantation) |
| Hepatitis B | Prevention of HBV infection (e.g., liver transplant) |
| Rho (D) | Prevention of haemolytic disease of the newborn |

# Appendix-2 Prescreening Checklist for biological registration dossier

#  Appendix – 3 Check List for Export of plasma for Fractionating Factory

* Each plasma container is packed in such a way as to maintain complete labeling information and easily traceable during any stage of transportation.
* The shipping documentation should include
	+ dated shipping document signed by responsible person
	+ certificate of origin and control of the plasma, stating for each donation the
	+ collection date;
	+ carton number;
	+ results of virology and immunohematology screening;
	+ test kits used and their batch number;
	+ signature of the director or an authorized person;
* Password-protected electronic file of the plasma donations and samples sent, stating for each donation collection date (this needs to be agreed with the fractionator):
	+ carton number;
	+ results of virology and immunohematology screening;
	+ test kits used and their batch number;
* Data logger for continuous temperature monitoring and recording of temperature during transportation (to be verified by fractionator, assuring the shipping condition of plasma is maintained).
* Copy of Invoice for custom purpose only.

Appendix – 4 Check List for Clearance of Import Cases

 **(for import of fractionated product as FG)**

|  |  |
| --- | --- |
| **DY # & DATE ►**(FOR OFFICIAL USE ONLY) |  |
| **NATURE OF CONSIGNMENT** (PLEASE TICK THE RELEVANT BOX) |
| **RAW MATERIAL** □ | **FINISHED /SAMI FINISHED DRUGS** □ | **PACKING MATERIAL** □ |
| **NAME & ADDRESS OF IMPORTER** (IN BLOCK LETTERS) **▼** | **NAME & ADDRESS OF EXPORTERS** (IN BLOCK LETTERS)**▼** |
| **NAME OF RAW MATERIAL / FINISHED DRUG/ PACKING MATERIAL IMPORTED** (IN BLOCK LETTERS) |  |
| **INVOIVE # & DATE ▼** | **QUANTITY ▼** | **PER UNIT PRICE / RATE ▼** | **TOTAL VALUE ($)▼** |
| **S.NO.** | **Documents** | **Original** | **Photo-copy** | **Remarks** |
|  | Form -8 (Rule 14 (f)) | □ | □ |  |
|  | Form -1 (Rule 3(ii))(FOR FINISHED DRUGS ONLY) | □ | □ |  |
|  | Form-3 (Rule 5(i)) | □ | □ |  |
|  | Copy of Valid D.I.L (Form 5) (Rule 7) | □ | □ |  |
|  | Copy of Registration & renewal status (Section 23 of Drug Act) | □ | □ |  |
|  | Copy of License (DML) & its Renewal/ Drug Sale License  | □ | □ |  |
|  | Form-7 (Rule 14(d)(i)) | □ | □ |  |
|  | Certificate of Analysis (Rule 14(d)(ii)) | □ | □ |  |
|  | Latest Testing Reference USP/BP/EU/JP etc. of raw material (if required) |  |  |  |
|  | Valid API manufacturing license (for APIs) and GMP Certificate of the exporting firms by respective Drug Regulatory Authority (Letter No. F.1-10/2016-Add: Dir (R.I)/M-264 dated 30th March,2017 | □ | □ |  |
|  | Packing list | □ | □ |  |
|  | B.L / A.W.B | □ | □ |  |
|  | Consumption details of previous consignment (if required). | □ | □ |  |
|  | Any other document (s) Particularly Required (Please Specify in remarks columns) | □ | □ |  |
|  | Invoice (2 sets) with clearance certificate (2 sets) | □ | □ |  |
|  | %age of Remaining shelf life(AS PER IGM DATE)(Period from arrival in Pakistan to expiry date X 100 ÷ Total life = remaining shelf life in %age= \_\_\_\_ %) | □ | □ |  |
|  | Name of ware house Pharmacist | □ | □ |  |
|  | Undertaking in case of submission of photocopies | □ | □ |  |
|  |  Any exemption obtained from labelling and packaging rules | □ | □ |  |
|  | Duly signed stamped Consumption details of previous consignment along with undertaking of genuineness of consumption statement if the is raw/ packaging material falls in any of the FBR/ Customs concessionary SRO.  | □ | □ |  |
|  | Fee challan R.S./- 2000 as per S.R.O. 526(I)/2021, dated 30-04-2021 | □ | □ |  |