



ETHIOPIAN FOOD AND DRUG AUTHORITY

GUIDELINE FOR REGISTRATION OF PLASMA DERIVED MEDICAL PRODUCTS

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1. Introduction

The Ethiopian Food and Drug Authority (EFDA), under Proclamation 1112/2019, regulates all medicinal products, including plasma-derived biological products. Article 30(3) of the proclamation mandates that blood and blood components intended for transfusion or further processing must comply with stringent safety and quality standards before use.

Plasma-derived medicinal products, derived from human blood, are critical for diagnosing, treating, and preventing diseases. Due to their biological nature, these products exhibit inherent variability, necessitating complex manufacturing and control processes. Advances in protein purification technology (fractionation) have expanded the availability of these products globally, but the risk of viral transmission remains a concern. Manufacturers are responsible for ensuring product safety, quality, and efficacy through state-of-the-art technologies.

Applicants seeking market authorization for plasma-derived medicinal products must demonstrate compliance with good manufacturing practices and provide comprehensive data to prevent raw material contamination and ensure effective virus removal. This includes submitting detailed manufacturing and control information for both raw materials and finished products, in line with Common Technical Document (CTD) requirements.

The EFDA evaluates submitted dossiers against local and international standards to minimize the risk of infectious disease transmission. The authority ensures the quality, safety, and efficacy of these products through rigorous assessment before granting marketing authorization. This guideline will be updated as new scientific advancements enhance the manufacturing and testing of plasma-derived medicinal products.

2. Scope

This guideline describes the technical requirements for the registration of plasma-derived medicinal products that are derived from human blood.

3. Definitions:

Plasma: is the liquid component of human blood, separated from other blood components, that serves as a raw material for the production of medicinal products. It is collected and processed under strict regulatory standards to ensure safety and quality, as mandated by the Ethiopian Food and Drug Authority (EFDA) under Proclamation number 1112/2019, for use in transfusion or further manufacturing into plasma-derived medicinal products.

Plasma derived medicinal products: are biological therapeutic agents manufactured from human plasma through complex processes such as protein purification (fractionation). These products are intended for the diagnosis, treatment, or prevention of diseases in humans and must comply with rigorous safety, quality, and efficacy standards, including advanced manufacturing and testing procedures to minimize risks like viral transmission, as required by the EFDA under Proclamation 1112/2019.

4. Requirements

4.1. Administrative and product information

4.1.1. Cover Letter

The applicant responsible for registration of plasma derived medicinal products should submit a signed and dated letter for submission of the dossier by mentioning the name and strength of product included in the dossier. The letter should indicate that the information provided in the dossier is true and correct.

4.1.2. Table Contents of the Dossier

Table Contents with page numbers should be provided.

4.1.3. Application Form

Completed and signed application form should be submitted as provided in Annex I of this Guideline.

4.1.4. Agency Agreement

The applicant should have agreement in accordance with the requirements indicated in the guideline for the registration of medicines.

4.1.5. Good Manufacturing Practice and Certificate of Pharmaceutical Product

The manufacturer should have a valid Good Manufacturing Practice (GMP) certificate issued from EFDA before market authorization is granted. However, the copy GMP certificate issued from the country of origin should be provided. Certificate of pharmaceutical product (CPP) should also be submitted in accordance with the format indicated in the guideline for the registration of medicines.

4.1.6. Lot release certificate

This refers to the lot release certificate issued by the regulatory authority or National Control Laboratories of the country of origin of the product responsible for its release. The certificate may include the following information:

- name and address of the manufacturer;
- site(s) of manufacturing;
- trade name and/or common name of product;
- marketing authorization number;
- lot number(s) (including sub-lot numbers and packaging lot numbers if necessary);
- type of container;
- number of doses per container;
- number of containers/lot size;
- date of start of period of validity (e.g. manufacturing date) and/or expiry date;
- storage condition;
- signature and function of the authorized person and the agent authorized to issue the certificate;
- the date of issue of the certificate;
- the certificate number.

4.1.7. Manufacturer's declaration

A document should be presented certifying that the information provided is the information corresponding to all the studies performed, regardless of their results. This should include all the pertinent information regarding all toxicological and/or clinical tests or trials of the plasma derived medicinal product that are incomplete or have been abandoned and/or completed tests related to indications not covered by the application.

4.1.8. Regulatory Status in Other Countries

The countries where this product has been registered and marketed, and withdrawn from the market should be listed.

4.1.9. Product Information

Product information including package insert, labeling, and summary of product characteristics (SmPC) should be provided. All product information label statements are required to be in Amharic or English. Any information appearing in the product information (labels, PIL, and SmPC) should be based on scientific justification.

4.1.10. Summary of product characteristics

Recommended format for the content of the SmPC is provided in the medicine registration guideline.

4.1.11. Labeling (immediate and outer label)

Only original labels or computer-ready color-printed (Artwork) labels are accepted for final approval. In the case where the text of the labels is printed directly on plastic packaging materials through a silk screen process, photocopies of these labels will be accepted for approval.

The titles for batch number, manufacturing, and expiry dates should be part of the printing (typewritten materials, stickers, etc., are not acceptable). If the labeling technology of the manufacturer is such that this information is to be printed on the label during production, a

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written commitment to show all the required information on the label of the finished product must be submitted. The contents of the label should at least contain:

- a. The name of the product- brand and generic/International Non-proprietary Name (INN);
- b. Pharmaceutical form and route of administration;
- c. Qualitative and quantitative composition of active ingredient(s), preservative(s), and antioxidant (s);
- d. The volume of the contents, and/or the number of doses, or quantity in container;
- e. Directions to consult the package insert or the carton label for complete directions for use;
- f. Handling and storage conditions;
- g. License number of the manufacturer;
- h. Batch number;
- i. Manufacturing date;
- j. Expiry date; and,
- k. Name and address of manufacturer.

4.1.12. Patient Information Leaflet (PIL) or Package Insert

The general content of the PIL should be prepared in line with the content of the SmPC. The PIL should not be described or presented in a manner that is false, misleading, or deceptive or is likely to create an erroneous impression regarding its use in any respect, either pictorially or in words.

4.1.13. Evidence for an Application Fee

Each application should be accompanied by a relevant service fee for registration. Applicants are advised to contact the Authority for the amount and details of mode of payment.

5. Technical Requirements

5.1. Drug Substance

5.1.1. Plasma Master File (PMF)

The plasma master file is a standalone document and should be filed separately with the application.

The following data requirements should be submitted as a standalone document:

Plasma source and collection;

- Epidemiological data on blood transmissible infections;
- Characteristics of donations and selection/exclusion criteria;
- Testing of blood/plasma donations and pools for infectious agents;
- Plasma quality and safety;
- Conditions of storage and transport of plasma; and
- A copy of the plasma specification and plasma pool batch analysis data.

However, if the source of the plasma-derived ingredient(s) is a third-party supplier, then it is the applicant's responsibility to procure the PMF from the PMF holder for submission to EFDA. The applicant may cross-reference an existing PMF for a product application if an updated PMF has been submitted to EFDA for another product application by the same product registrant. Reference to more than one PMF is possible and should be clearly indicated in the dossier.

Applicants are responsible for maintaining and updating the PMF annually: The PMF data must conform to the requirements recommended by EFDA's reference drug regulatory agencies (Stringent Regulatory Authorities) and in particular, the following documents and their subsequent revisions:

- Guideline on Plasma-derived Medicinal Product (Current version of EMA/CHMP/BWP/706271/2010);
- Guideline on the Scientific Data Requirements for a Plasma Master File (PMF) Revision 1 (CPMP/BWP/3794/03 Rev. 1); and
- Annexes to Guideline on the Scientific Data Requirements for Plasma Master File (PMF).

5.1.2. The PMF document requirements include:

- a. Documents verifying that each donor of source material has undergone a proper screening procedure and has met all established health criteria (including viral risks requirements). The criteria used must conform to the recommendations on suitability of blood and plasma donors set out by the US FDA, EMA, WHO and other stringent regulatory authorities. The following details need to be provided:
 - i. Collection centers
 - Names and addresses of blood/plasma collection centers, including sub-contractors and any separate site for the testing of individual donations;
 - Audits: Internal audits (frequency, date of last audit and final outcome of last inspection); and
 - Audits by regulatory authority (frequency, date of last audit and final outcome of last inspection).
 - ii. Epidemiology data on blood-borne infections
 - Provide an assurance that there is a continuing evaluation of the epidemiology at collection centers; and
 - Data should be reported as:
 - Incidence of confirmed seroconversion rates in regular donors (per number of donors and number of donations); and
 - Prevalence of confirmed positives in new donors and known donors.
 - iii. Selection/exclusion criteria
 - Characteristics of donation:
 - Indicate whether or not a plasma donor is remunerated;
 - Clarify the nature of any compensation for donation; and
 - Outline the nature of the examination and interview of donors; and
 - iv. Exclusion criteria for donors:
 - Confirm that centers do not collect blood/plasma from a population with a high prevalence of infections transmitted by blood (HIV, HCV, HBV etc.);
 - Confirm that there are measures taken to ensure viral safety for recipients with respect to major pathogenic agents; and

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- Compliance with those exclusion criteria specified in appropriate documents (Directives, Guidelines, Pharmacopoeia).
- b. Documents verifying that each unit of source material has been tested non- reactive for Hepatitis B surface antigen, anti-HIV-1&2 by NAT (Nucleic Acid Test), anti-HCV by NAT and other test parameters as recommended by US FDA, EMA, WHO or an equivalent SRA. The following details need to be provided:
- i. Screening tests for markers of infection:
 - List of tests performed on individual donations;
 - License number of each test kit used;
 - Validation of these screening procedure methods; and
 - Details of any inventory hold/ quarantine periods and procedures.

ii. Characterization of plasma pools

If minipools of donations are tested, the size of the minipools, rationale and full details of the testing should be provided. In case the minipools/pools are not tested in the same way (i.e. different size of minipool, different viruses tested), the different strategies should be described.

- c. Documents verifying that all steps in the processing of source material, including donor examination, blood collection, plasmapheresis, laboratory testing, labelling, storage, and issuing, are performed in centers that have been licensed by the NRA or equivalent authority for that purpose. The centers must conform to the requirements for the collection of source materials as specified in “The Collection, Fractionation, Quality Control, And Uses of Blood and Blood Products published by the WHO”. The following details need to be provided:
- i. System to trace the path of any donation:
 - Confirm that there is a system in place that ensures traceability from the donation center to finished product and vice versa; and,
 - Provide information on steps that would be taken if it is found retrospectively that the donation(s) should have been excluded from processing.

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- ii. Documents that verify the fractionator/manufacturer and donation center(s)/organization responsible for collecting plasma complies with current GMP principles; and
- iii. Letter of commitment from the manufacturer stating that:
 - All collection centers have signed the contract; and
 - The national authority will be notified in the event of a serious failure at a blood collection center.
- d. Documents verifying that all source materials are collected by aseptic techniques designed to assure the integrity and minimize the risk of contamination of the source material. The documents should also verify that the closure of the container used maintains a hermetic seal. The following details need to be provided:
 - i. (i) Blood bags
 - Information on the name of bag, manufacturer, anticoagulant solution, composition and specification; and
 - Indication on conformance to a particular standard (e.g. WHO, Ph.Eur.).
 - ii. Plasma quality
 - Plasma specification
 - Information on specification(s) and confirm compliance to specification(s); and
 - Information on in-process tests on the plasma pool, if any.
 - Confirm compliance with the Ph Eur Monograph for Human Plasma for Fractionation and with any requirements for particular products for which Ph Eur Monographs exist.
 - Information on storage conditions and maximum storage time with an indication on how conditions are maintained from collection center to the manufacturer; and
 - Description of the conditions for processing, including freezing and storage of plasma for every collection and processing centers.
 - Confirm validation of the freezing conditions.

- e. Documents verifying that the source materials do not contain any additives other than citrate or acid citrate dextrose anticoagulant solution, unless it has been shown that the processing method yields a final product free of the additive to such an extent that the continued safety, purity, potency, and effectiveness of the final product is not adversely affected.

5.1.3. Intermediates

An intermediate plasma fraction (intermediate) is the partially fractionated starting material which must undergo further manufacturing steps before it becomes a bulk product or final product. Intermediates, commonly used for further processing into a final product, are fractions recovered from the process for the production of clotting factors (e.g. cryopaste) or from the production process of immunoglobulins or albumin (e.g. fractions II, III, IV, V), and may be prepared and stored by the product manufacturer or obtained from another supplier (e.g. a contract manufacturer).

The collection and control of starting materials for the production of an intermediate plasma fraction are important factors in the assurance of its quality. Information up to and including the production of the plasma pool should be provided in the PMF or in part 3.2.S of the dossier. This information should be provided to the manufacturer of the finished product. A contract should be established between the supplier of the intermediate and the manufacturer of the finished product. This contract should address information from the manufacturing process, traceability and specifications of the plasma and the intermediate, and the storage and transport of the intermediate. The product applicant has final responsibility for the quality and safety of the plasma derived medicinal product.

5.1.4. Manufacturing Process and Control

Data requirements for plasma-derived medicinal products should be documented as described in the various sections of the guidance documents (latest versions) listed below:

Collection, Processing & Control:

- WHO Recommendations for the Production, Control and Regulation of Human Plasma for Fractionation.

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- WHO Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives. Updated version of the WHO Technical Report Series No. 840, Annex 2
- Guideline on Plasma-derived Medicinal Products (EMA/CHMP/BWP/706271/2010)

Viral Inactivation: describe little about viral inactivation and then let them to refer more on

- WHO Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products. Technical Report Series (TRS) No. 924, Annex 4 (Adopted by ECBS 2001)
- Note for Guidance on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin (CPMP/ICH/295/95).
- Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses (CPMP/BWP/268/95).

The following data should be filed under the various 3.2.S sections of the CTD:

- a. Documents that verify all steps in the manufacture of the final product are conducted in establishments licensed by the NRA or equivalent authority for that purpose. All handling and processing techniques employed should conform to the current relevant international GMP guidelines.
- b. Documents verifying that each batch of source material intended for manufacture has been tested for Hepatitis B surface antigen, antibody to HIV1&2 and antibody to Hepatitis C Virus by FDA officially recognized pharmacopeia. Each batch of source material must also be tested for HCV RNA by genomic amplification testing. The following details need to be provided:
 - i. Plasma pooling**
 - Information on the number of individual plasma units pooled together;
 - List of tests performed on these plasma pools; and
 - License number for each test kit used.
- c. Documents verifying that the processing method used does not affect the integrity of the product and has been demonstrated to consistently yield a product that is safe for

use in humans. Processing methods used for the manufacture of intravenous products should have been shown to consistently yield a product that is safe for intravenous injection.

- d. Documents verifying that processing steps are conducted to minimize the risk of contamination from pyrogens, micro-organisms, or other impurities. Preservatives to inhibit the growth of micro-organisms should not be used or added to the product at any stage of processing. The following details need to be provided:

5.1.4.1. **Manufacturing process**

A detailed description of the manufacturing process and controls to demonstrate proper quality control or prevention of possible contamination with adventitious agents:

- Starting materials: Information on raw materials, intermediate products, reagents and auxiliary materials with specifications or statements of quality of each;
- Flowchart: A complete visual representation of the manufacturing process flow. This flow should show the production steps, equipment, and materials used, along with a complete list of the in-process controls and tests performed on the product at each step. This diagram should also include information on the methods used to transfer the product between steps;
- Detailed description: A detailed description of the fractionation, formulation, sterilization, purification and aseptic processes. This should include a rationale for the chosen methods, and the precautions taken to assure containment and prevention of contamination or cross-contamination. In-process bioburden and endotoxin limits should be specified where appropriate. Any reprocessing or related method should be fully validated and described. The allowable conditions for reprocessing of all or parts of any batch should be described; and
- Batch record: A complete batch record of the process of production of the biologic product should be included.

5.1.4.2. **Process control**

- A description of the control checks performed at various stages of the manufacture, processing and packaging of the product;

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- A description of the in-process and final controls, including analytical tests and appropriate data to support the specifications; and
- Validation data:
 - A description of the validation studies, which identify and establish acceptable limits for critical parameters to be used as in-process controls, to assure the success of routine production;
 - Validation studies for the purification process: a description of the validation of the purification process to demonstrate adequate removal of extraneous substances such as chemicals used in purification, column contaminants, endotoxin, antibiotics, residual plasma proteins, non-viable particulates and viruses; and
 - Validation studies for all sterilization and aseptic processes (e.g. formulation through filling and sealing).

5.1.5. Notes on process steps for inactivation and removal of viruses

- Procedures specifically designed to inactivate or remove infectious viruses should be clearly defined, justified and documented. In addition, recent transmissions of both enveloped and non-enveloped viruses by certain plasma-derived products have highlighted the need for a strategy to further increase the assurance of viral safety of these products;
- When necessary, a viral risk assessment should be performed via calculation of the estimated risk per dose, as outlined in the Guideline on Assessing the Risk for Virus Transmission – New Chapter 6 of the Note for Guidance on Plasma-derived Medicinal Products (CHMP/BWP/5180/03). The risk assessment should demonstrate that the virus inactivation/removal capacity clearly exceeds the potential amount of virus that could enter the production process;
- The following document, and its subsequent revisions, should also be referred to:
 - Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses (CPMP/BWP/268/95); and
- The following notes are provided as a general guide:

- Albumin (Human Solution and Plasma Protein Fraction [Human] Solution) – the product must have undergone heat treatment or other established viral inactivation procedures. Heat treatment should be conducted so that the solution is heated continuously for not less than 10 or more than 11 hours at an attained temperature of $60 \pm 0.5^{\circ}\text{C}$.
- Clotting Factor Concentrate, Intravenous Immunoglobulin and Intramuscular Immunoglobulin – the product must have undergone processing methods that include established and validated specific viral inactivation capable of inactivating at least 10^5 infectious particles of HIV per mL of solution (i.e. a $5\log_{10}$ reduction in concentration of viable virus), and not transmit viral hepatitis.

5.1.6. Stability of the drug substance

Stability studies should be performed, taking into account ICH guidelines, especially “Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological products” (Q5C). The MAH/supplier should ensure that stability studies on the biological drug substance or intermediate and, unless otherwise justified, on the finished product are performed if an intermediate from an external manufacturing site is introduced.

5.2. Drug Product

The following data should also be filed under the various 3.2.P sections of the CTD (Module 3 of ICH CTD).

5.2.1. Manufacturing process

The strategies used in the manufacture of plasma-derived medicinal products are critical for product quality, safety and efficacy. Manufacturing strategies vary according to product and manufacturer, and usually include several fractionation/purification procedures, some of which may also contribute to the inactivation and/or removal of potential adventitious agents. Additionally, specific procedures to inactivate/remove viral contaminants should be a requisite part of the manufacturing strategy for all plasma products. Plasma-derived medicinal products are defined largely by reference to their method of manufacture, as with biological medicinal products in general. Therefore, the use of alternative processes is usually not acceptable.

While selection of donors and testing of donations are essential safety measures, incidents of virus transmission show that they are insufficient alone to ensure safety of the product. The manufacturing process itself plays a central role and is of great significance for products derived from plasma. Studies of a process for the ability to inactivate or remove virus infectivity will be subject to particularly careful evaluation when products derived from blood or plasma are considered. This will include consideration of the reduction in virus titre achieved, the rates of inactivation and the shape of inactivation curves, how robust the step is to process variables, and whether virus inactivation or removal is selective for a particular kind of virus.

The suitability of the various materials and procedures used in manufacture as well as the selected operating conditions, parameters and tolerances should be validated by correctly designed and interpreted studies.

5.2.1.1. Fractionation/purification procedures

5.2.1.1.1. Precipitation methods

Physical methods

Cryoprecipitation is most often used as the initial step for the production of Factor VIII concentrates. Subsequent purification techniques for FVIII include precipitation, adsorption of other coagulation factors, and chromatographic separation as well as procedures for virus inactivation to obtain the finished products. Cryoprecipitate-depleted plasma is commonly used for the preparation of other coagulation factors by adsorption/elution or chromatographic procedures and the residual plasma can be further processed to yield immunoglobulins and albumins.

Physical/chemical methods

Among these methods, the ethanol fractionation procedures derived from the Cohn method are the most widely used for albumin and immunoglobulins. They commonly incorporate several steps, in each of which compliance with specific requirements is decisive for product quality; some of these steps may also contribute to effective reduction of potential viral contaminants (see also below). Therefore, clear specifications for ethanol and protein concentration, temperature, pH and ionic strength, and time of treatment, with data on acceptable tolerance as

well as the means of controlling them should exist. Appropriate data should also be provided for methods relying on other chemical agents such as ethylacridin-lactate, caprylic (octanoic) acid, methanol, ammonium sulphate, polyethylene glycol, cationic detergents, which are sometimes used in the preparation of certain plasma derivatives, as a rule in combination with other purification procedures. Some of these substances may have an impact on virus safety such as caprylic (octanoic) acid, for others information is still scarce.

5.2.1.1.2. Chromatographic methods

A number of different chromatographic procedures may be used in the purification and manufacture of plasma-derived medicinal products. It has to be taken into account that the selectivity of the procedures and the yields depend critically on the quality of the chromatographic resins as well as on factors like the capacity of the column, nature and concentration of proteins in the product, ionic strength and the pH of buffers, flow rate, contact time and temperature. The chosen procedures should be based on data of process development studies. All appropriate specifications and accepted tolerances should be stated, and control data documented.

The conditions of storage of the columns, preservation and elution of preservatives, sanitization and methods of regeneration should also be described. Details should be given of clarification and sterile, dia- or ultra-filtration procedures used.

5.2.1.1.3. Additional Considerations

Anticoagulants such as antithrombin and heparin may be added as raw materials/reagents at various stages during the production of coagulation factors to minimize activation. The materials, their use and residual concentrations in the final product should be documented. The residual concentrations should be measured in the final product unless acceptable and consistent results have been demonstrated. Several other compounds like charcoal, bentonite, colloidal silica are sometimes used for clearing various impurities like pigments, lipoproteins etc. Details on the characteristics of the compounds, on their decontamination and on the operating conditions should be provided.

5.2.1.2. Virus inactivation/removal procedures

Procedures to inactivate/remove infectious viruses are included in the manufacturing strategies for plasma-derived medicinal products. The manufacturing process conditions and in-process monitoring for virus inactivation/removal steps should be clearly defined and justified. Careful validation is needed for each inactivation/removal step ensuring that the validation includes worst case conditions. The integrity of the product should be demonstrated under established manufacturing conditions. For further information, reference is made to section 8 Adventitious Agents. It is essential that material that has been subjected to a virus inactivation/removal step should be segregated from untreated material to prevent cross-contamination (GMP principle).

5.2.1.3. Process Validation

Validation studies should be carried out by each manufacturer for the specific processes used and, unless otherwise justified, for each production site. Moreover, if studies involve modelling the process on a reduced scale, they should be capable of mimicking satisfactorily the conditions of full scale production and the suitability of the modelling should be demonstrated. For the principles of pharmaceutical development of the drug product, reference is made to the Note for Guidance on Development Pharmaceutics for Biotechnological and Biological Products CPMP/BWP/328/99 (Annex to Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96)). In the development of the manufacturing process, critical parameters and critical controls should be identified and controlled. This is particularly important for novel process designs, including new designs for products traditionally manufactured using ethanol fractionation. The general principles of the Note for Guidance on Process Validation (CPMP/QWP/848/96) are useful in this work, although the plasma derived medicinal products are not included in the scope of the guideline. The effectiveness of a given manufacturing process in consistently yielding a product with expected quality and biological activity should be documented with data based on a broad set of relevant analytical methods. Particular attention should be paid to demonstration of removal of process- and product-related impurities, for example chemicals used for, or derived from fractionation/purification procedures, and naturally occurring substances which may be hazardous, such as blood group substances and activated coagulation factors. Spiking experiments with certain potential contaminants may be necessary to demonstrate the clearing efficiency of the process. The studies should be designed to justify

the selected operating conditions and the acceptable tolerances, including worst case conditions, and to document their adequacy in achieving the expected process performances. When chromatographic columns are used, conditions leading to overloading as well as leaching from the gels, particularly in the case of affinity chromatography with potentially harmful ligands, should be carefully investigated. Attention should also be paid to the cleaning and regeneration of the columns with particular emphasis on pyrogen elimination and virus carry over. The criteria for the use and re use of chromatography resins and their life time should be provided. This is also applicable to filters in case of re-use. For the establishment of release specifications, reference is made to the general principles laid out in the Note for Guidance on Specifications: Test procedures and Acceptance Criteria for Biotechnological/Biological Products (CPMP/ICH/365/96). The manufacturer should demonstrate consistency at full scale production, showing compliance with the established specifications of the product. To this aim, batches should be derived from different bulks. In case that the manufacturing process starts from different amounts of plasma, it should be shown that the process yields a comparable product under the range of conditions applied. If a manufacturer decides to use intermediates from different manufacturing sites it should be shown that comparable products are consistently obtained. In the case of different manufacturing sites used in parallel a detailed validation program should be presented to demonstrate consistency. Reprocessing should only be performed in case of process failures. The procedures and criteria should be fully described. Validation data should demonstrate that repetition has no negative influence on product quality.

5.3. Quality control

The physical, chemical and pharmaceutical properties of the finished product must comply with EFDA officially recognized pharmacopoeias such as the United States, British, European and international Pharmacopoeia. The following details need to be provided:

a. Product testing

- Specifications and analytical methods used for release testing and expiration dating to assure product identity, purity, strength or potency and lot-to-lot consistency
- Validation protocol and results for non-compendial analytical systems to demonstrate system suitability;

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- Lot release protocols, including specification ranges of representative lots of the product. Specifications may include, but are not limited to, biochemical purity, safety, appearance, pH, residual moisture, excipients, endotoxins, and sterility; and
- Methods and standards of acceptance, including the sampling plan and the accuracy and precision of the analytical methods in sufficient detail to permit duplication and verification.

b. Container closure system/shipping containers

A description of the container and closure system with information on its compatibility with the biological substance; and evidence of container and closure integrity.

c. Stability

Stability data for the product as packaged in the registered container closure system;

- A description of the storage conditions, study protocols and results supporting the stability of the product and any intermediates that are stored;
- An expiration date supported by the results of the stability study; and
- When used as an excipient in therapeutic products, the expiry date of the plasma-derived product should not be earlier than that of the finished product. It is recommended that the manufacturers have a system in place to maintain traceability and notifications regarding post-collection information; and
- The package insert should include warning statements as per Guideline on the warning on transmissible agents in summary of product characteristics (SmPCs) and package leaflets for plasma-derived medicinal products (CHMP/BWP/360642/2010).

5.4. PMF Life Cycle Management

Applicants are responsible for keeping the PMF updated. The updates are to be submitted annually. If a currently-registered PMF contains an update or amendment, the product registrant is responsible for updating EFDA accordingly:

1. If the update/amendment is a significant change (e.g. significant changes to the plasma processing), then the update should be submitted as soon as it is made known; OR

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2. If the update/amendment is not a significant change (e.g. a change of collection centers), then it can be submitted as part of the annual update.
3. Please note that if significant changes are implemented before the next annual update, then an updated PMF needs to be submitted.

6. References

1. [Guideline on plasma-derived medicinal products](#)
2. [Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives, Annex 2, TRS No 840](#)
3. [Scientific data requirements for plasma master file - Scientific guideline | European Medicines Agency \(EMA\)](#)