FOOD AND DRUGS AUTHORITY

GUIDELINES FOR REGISTRATION OF PLASMA DERIVED MEDICINAL PRODUCTS

Document No.	**:FDA/SMC/BPD/GL-PDP/2019/10**
Date of Adoption	**:15th March, 2019**
Effective Date	**:15th March, 2019**
Version No.	**:01**

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1.0 INTRODUCTION

Human plasma contains many proteins which, following extraction, purification, and formulation into medicinal products are of great medical importance

The manufacture has the responsibility to assure the quality, safety and efficacy of Plasma Derived Medicinal Products (PDMPs) manufactured in its manufacturing facility. The Food and Drugs Authority's (FDA) guidelines for the registration of PDMPs provide guidance to applicants intending to register their product in Ghana. In addition, the guidelines publish the required format and content for submitting a PDMP registration application to the FDA, and further provide guidance that ensure that products and manufacturers meets the minimum established regulatory requirements to do business in Ghana.

PDMPs are products of human or animal origin, which exhibit some intrinsic variability. They are characterized by complex manufacturing and control processes. Improvements in protein purification and molecular separation technology have made available a wide variety of products, however, the potential for viral transmission remain real. As a result registration application submissions shall be expected to include modern technologies and methods designed to minimize contamination of starting raw plasma. Solely testing the final product alone cannot assess their quality; hence, a complete product development dossier, in addition, to a satisfactory current Good Manufacturing Practice (cGMP) audit of the manufacturing facility shall be required to make a regulatory decision.

The FDA fully evaluates all data and information submitted on the quality, safety and efficacy profiles of PDMP application for completeness, and in line with requirements contained in these guidelines. The FDA shall register the product and grant marketing authorization following satisfactory evaluation outcome.

These guidelines provide guidance on the requisite data and information that is needed in an application dossier, and evidence to show that the product

development pathway contains information on the various stages of development; research, product development, production, quality control, and non-clinical and clinical studies, and guarantees that the quality, safety and efficacy required of the PDMP to be used in humans has been established.

As precautionary measures to minimize the risk of transmission of infectivity by PDMP's, the FDA shall revise these guidelines from time-to-time in consultation with the National Blood Service Ghana to capture new and emerging agents or markers.

1.1 SCOPE

This guidance document describes the regulatory information and requirements for the registration of plasma derived medicinal products.

This guideline is applicable to all plasma-derived medicinal products containing an active or inactive ingredient that is derived from human blood. Because such products carry the risk of transmitting infectious agents, the safety of these products is assured through the requirements as described in this guidance document.

1.2 SCIENTIFIC GUIDELINES APPLICABLE TO ALL PLASMA DERIVED DICINAL PRODUCTS

Where specific guidelines are unavailable, the FDA will adopt the Committee for Medicinal Product for Human Use (CHMP) Guidelines, which are available at the following websites EMEA: http://www.emea.europa.eu and International Conference of Harmonisation (**ICH**) Guidelines: http://www.ich.org

2.0 GLOSSARY

- **"Authority"** means Food and Drugs Authority
- **"Applicant"** means the product owner or license holder. Representatives of license holders may not hold themselves as applicants unless they own the product.
- **"Accelerated stability studies"** means studies designed to determine the rate of change of vaccine properties over time as a consequence of the exposure to

temperatures higher than those recommended for storage. These studies may provide useful support data for establishing the shelf-life or release specifications but should not be used to forecast real time real condition stability of a vaccine. They could also provide preliminary information on the vaccine stability at early developmental stages and assist in assessing stability profile of a vaccine after manufacturing changes.

- **Batch or lot:** set of final packages of finished vaccine, hermetically sealed, that is homogeneous with respect to the risk of cross-contamination during the packing and freeze-drying processes. Therefore, all final packages must have been filled from a single set of ingredients in a single working session and, if applicable, freeze-dried in standardized conditions in the same room.
- **Carrier protein:** a protein used mainly in conjugated polysaccharide vaccines to which the polysaccharide antigen is linked in order to improve both the magnitude and type of the immune response.
- **Clinical particulars**: These are indications for use, contra-indications, undesirable effects (with reference to frequency and seriousness), precautions for use, dosage and method of administration, overdose, special warnings, major and minor incompatibilities (If appropriate), special precautions during administration of the product, first aid and safety directions.
- **Country of origin:** it corresponds to the country where the legal certifications of the product are generated.
- **Dosage form:** the physical form in which a product is prepared for administration to the recipient.
- **Shelf life:** it is the date before which the quality of the vaccine remains acceptable for its intended use as outlined in the market authorization. It is established based on stability studies.
- **Variation** means a change in the indication(s), dosage recommendation (s), drugs classification and / or patients group(s) for a previously registered biological product been marketed under the same name in Ghana. A variation

also includes, but not limited to, a change in the product name, site of manufacture and / or source of ingredients.

- **Validation** means series of documented procedures or actions, consistent with good manufacturing practices, demonstrating that the processes, equipment, materials, activities and/or systems satisfy the predetermined specifications and quality attributes.
- **"Well-resourced or reference National Regulatory Authority"** means a member of ICH prior to 23 October 2015, namely: the US Food and Drug Administration, the European Commission and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; or an ICH observer prior to 23 October 2015, namely: the European Free Trade Association, as represented by Swissmedic and Health Canada; or a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement prior to 23 October 2015, namely: Australia, Iceland, Liechtenstein and Norway.

3.0 REQUIREMENTS

3.1 ADMINISTRATIVE STATUS OF THE PRODUCT

The legal information accompanying the dossier should be duly certified and authenticated under the procedure in effect in the country of origin, and issued by the appropriate entity.

3.1.1 Qualified person responsible for the product release (under the country's legislation).

Applicants shall be required to submit a document issued by the manufacturer of the product giving information on the individuals responsible for the product release. The information should include the identity and designation of the authorized person in charge of regulatory activities.

3.1.2 Certificate of Pharmaceutical Product (CoPP)

Using the World Health Organization's (WHO) model, this certificate includes information on compliance with Good Manufacturing Practices (GMP). A free

sale certificate where applicable should be submitted in addition to the GMP certificate.

3.1.3 Certificate of Good Manufacturing Practices (GMP) of other manufacturers involved in the production of the product

This should include manufacturers that are involved in any stage of the production process, for example manufacturer(s) of the active ingredient(s), the diluents, and those responsible for labelling and packaging of the finished product. It is important that the certificate indicates the procedures that the establishment is authorized to perform.

3.1.4 Trademark certificate (optional)

Proposed brand name and art work for primary and secondary labels. These should be submitted for approval by FDA prior to submission of application, dossier and samples for registration

3.1.5 Invention patent certificate (based on the country of origin's legislation)

3.1.6 Batch release certificate

Refers to the batch release certificate issued by the regulatory authority of the country of origin of the product or the regional regulatory authority responsible for its release. The certificate should correspond to those samples submitted with the application for registration. Please refer to the FDA website for the minimum requirements (batch release document).

3.1.7 Lot release certificate

Refers to the lot release certificate issued by the regulatory authority of the country of origin of the product or the regional regulatory authority responsible for its release. The certificate should correspond to those samples submitted with the application for registration.

3.1.8 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 biological product that are incomplete or have been

abandoned and/or completed tests related to indications not covered by the application.

The Ghana Food and Drugs Authority recommends that applicants intending to develop plasma derived medicinal products should meet with regulators at the FDA to present their product development plans and establish a schedule of milestones that will serve as standards for future discussions with the Authority.

3.2 GENERAL REQUIREMENTS OF THE DOSSIER

The product development dossier should be:

3.2.1 Submitted in English

3.2.2 Where originals are in another language, copies should be presented together with certified English translations.

3.2.3 Be complete as per the specifications detailed in this guideline

3.2.4 Containing a table of contents, the flow of information must be as per the flow of the document requirement in this guideline

3.2.5 Indexed to the various appendices

3.2.6 Numbered on every page

3.2.7 Applications shall be submitted electronic format: two (2) copies, either saved on a USB flash drive or on a CDs

3.2.8 Contain certificates or testimonies obtained from other agencies or authorities in original or in case of duplicate or electronic submission, attested by the Public Notary or a Court of Justice

3.3 REQUIREMENTS FOR REGISTRATION /MARKETING AUTHORIZATION RELIANCE

Regarding products that have already been approved by a well-resourced NRA, the FDA shall activate the reliance pathway to facilitate regulatory decisions either on a case-by-case basis or at the explicit request of the Applicant. The Applicant shall submit the full Common Technical Document (CTD) dossier and the full Assessment reports of the CTD submitted to the well-resourced National Regulatory Authority (NRA) for approval. The application shall be identical to that submitted, evaluated and approved by the well-resourced NRA or reference NRA.

3.4 SPECIFIC REQUIREMENTS

3.4.1 Drug Substance

3.4.1Plasma 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 the FDA. The applicant may cross-reference an existing PMF for a product application if an updated PMF has been submitted to the FDA 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.

3.4.2 PMF Data Requirements.

The data must conform to the requirements recommended by FDA's reference drug regulatory agencies and in the ICH region and other well-resourced NRAs, the following documents and their subsequent revisions:

FDA guidelines for the registration of Biological Products

FDA guidelines for Blood Facility licensure and Product listing

Guideline on Plasma-derived Medicinal Products

(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)

The PMF document requirements include:

3.4.2.1 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 FDA/ National Blood Service Ghana. The following details need to be provided:

- **Collection centers**
  - Names and addresses of blood/plasma collection centres, 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).
- **Epidemiology data on blood-borne infections**
  - Provide an assurance that there is a continuing evaluation of the epidemiology at collection centres; 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.
- **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
- **Exclusion criteria for donors:**
  - Confirm that centres 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
- Compliance with those exclusion criteria specified in appropriate documents (Directives, Guidelines, Pharmacopoeia).

3.4.2.2 Documents verifying that each unit of source material has been tested nonreactive for Hepatitis B surface antigen, core antibody, anti-HIV-1 & 2 by NAT, anti-HCV by NAT and other test parameters as recommended by regulatory authority in country of origin. The following details need to be provided:

- 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.
- Characterisation 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.

3.4.2.3 Documents verifying that all steps in the processing of source material, including donor examination, blood collection, plasmapheresis, laboratory testing, labeling, storage, and issuing, are performed in facilities that have been licensed by the National Regulatory Authority or equivalent authority for that purpose. The centres must conform to the requirements for the collection of source materials as specified in document titles “The Collection, Fractionation, Quality Control, and uses of Blood and Blood Products” published by the WHO. The following information shall be provided:

- System to trace the path of any donation:
  - Confirm that there is a system in place that ensures traceability from the donation centre 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.

3.4.2.4 Documents that verify the fractionators/manufacturer and donation centre(s)/ organisation responsible for collecting plasma complies with Pharmaceutical Inspection Co-operation Scheme (PIC/S) Good Manufacturing Practices (GMP) and procedures; and

- Letter of commitment from the manufacturer stating that:
  - All collection centres have signed the contract; and
  - The national authority will be notified in the event of a serious failure at a blood collection centre.

3.4.2.5 Documents verifying that all source materials are collected by aseptic techniques designed to assure the integrity and minimise 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:

- 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.).
- 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 PhEur Monograph for Human Plasma for Fractionation and with any requirements for particular products for which PhEur Monographs exist.
- Information on storage conditions and maximum storage time with an indication on how conditions are maintained from collection centre to the manufacturer; and
- Description of the conditions for processing, including freezing and storage of plasma for every collection and processing centres.
- Confirm validation of the freezing conditions.

3.4.2.6 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.

3.4.3 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 registrant/applicant has final responsibility for the quality and safety of the therapeutic product.

3.4.4 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:

3.4.4.1 Collection, Processing & Control:

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

3.4.4.2 Viral Inactivation:

- 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:

- Documents that verify all steps in the manufacture of the final product are conducted in establishments licensed by the National Blood Service or equivalent authority for that purpose. All handling and processing techniques employed should conform to the current relevant international GMP guidelines of the National Blood Service, the EMACHMP or WHO.
- 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 tests approved for such use by the National Blood Service or an equivalent authority. Each batch of source material must also be tested for HCV RNA by genomic amplification testing.
- The following details need to be provided:

  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.
  - 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.
  - Documents verifying that processing steps are conducted to minimise 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:

    Manufacturing process

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

3.4.4.3 Starting materials: Information on raw materials, intermediate products, reagents and auxiliary materials with specifications or statements of quality of each;

3.4.4.4 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 method used to transfer the product between steps;

3.4.4.5 Detailed description: A detailed description of the fractionation, formulation, sterilisation, 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

3.4.4.6 Batch record: A complete batch record of the process of production of the biologic product should be included.

3.4.5 Process Control

- A description of the control checks performed at various stages of the manufacture, processing and packaging of the product;
- 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 sterilisation and aseptic processes (e.g. formulation through filling and sealing).

3.4.6 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 ±0.5^{o}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.

3.4.7 Drug Product

The following data should also be filed under the various 3.2.P sections of the CTD (Module 3 of ICHCTD or Part 2 of ACTD).

The physical, chemical and pharmaceutical properties of the finished product must comply with the relevant United States, British or European Pharmacopoeial requirements. The following details need to be provided:

- 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;
  - 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.
- 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.
- 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).

4.0 OTHERS

4.1 REGULATORY DECISION

When approved for registration, the product registration issued for a human plasma derived medicinal product will have the following post-approval registration conditions:

The import of the human plasma-derived medicinal product for therapeutic use, to which this registration relates, must be accompanied by a batch certification, including certificate of plasma origin and compliance. The batch certification and product movement records shall be maintained for three (3) years from the date of importation and be made available for inspection or upon request by the FDA

4.2 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 FDA accordingly:

4.2.1 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

4.2.2 If the update/amendment is not a significant change (e.g. a change of collection centres), then it can be submitted as part of the annual update.

4.2.3 Please note that if significant changes are implemented before the next annual update, then an updated PMF needs to be submitted

ANNEXURE

SANCTIONS

- The Authority shall cancel, suspend, or withdraw the registration of a drug if:
  - The information on which the drug was registered is later found to be false; or
  - The circumstances under which the drug was registered no longer exist.
- Any of the provisions under which the drug was registered has been contravened.
- The standard of quality, safety and efficacy, as prescribed in the documentation for registration is not being complied with.
- The premises in which the drug or part thereof is manufactured, packaged or stored by or on behalf of the holder of the certificate of registration is unsuitable for the manufacture, packaging or storage of the drug.
- Where the registration of a drug is suspended, withdrawn or cancelled, the Authority shall cause the withdrawal from circulation of that drug and shall accordingly cause the suspension, cancellation or withdrawal to be published in the Gazette.