APPENDIX 8 *GUIDELINE ON THE REGISTRATION OF HUMAN PLASMA-DERIVED THERAPEUTIC PRODUCTS*

This guideline[1] is applicable to all plasma-derived therapeutic 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 appendix along with the main guidance document.

1 DOCUMENTARY REQUIREMENTS

Applications for human plasma-derived medicinal products will be evaluated based on the products' quality, safety and efficacy. This guideline outlines the requirements for the Plasma Master File (PMF) and the specific quality documentation required to support registration of these products.

Documents pertaining to the collection and control of source materials should be provided as a standalone PMF. One set of the PMF should be submitted in softcopy in a CD/DVD (do not submit in hardcopy) together with the application dossier for the registration of a human plasma-derived product. Reference to the relevant PMF/s may be made in the following sections of the dossier:

(a) CTD section 3.2.S.2.3, if the PMF relates to a drug substance; or
(b) CTD section 3.2.R.1 (ICH CTD) or 3.2.Q.1 (ACTD), if the PMF relates to an excipient.

[1] Adapted from Guideline on Plasma-derived Medicinal Products (EMA/CHMP/BWP/706271/2010) and US FDA *Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-derived Biological Products, Animal Plasma and Serum-derived Products*

1.1 Body of Data – Drug Substance

1.1.1 Plasma Master File (PMF)

The plasma master file is a standalone document and should be filed separately from the application. When the information on plasma collection and control is available as part of the CTD dossier, this section of the dossier should be filed as a separate standalone document.

Once a plasma master file or a dossier section on plasma collection and control information is received as a separate standalone document, a PMF number will be assigned to the document.

For plasma collection and control information, which was previously submitted as part of section 3.2.S.2.3 of the dossier, the following information covering the data requirements according to the *PMF Data Requirements* section of this appendix 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 HSA. The applicant may cross-reference an existing PMF for a product application if an updated PMF has been submitted to HSA 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.

PMF Data Requirements

The data must conform to the requirements recommended by HSA's reference drug regulatory agencies and in particular, the following documents and their subsequent revisions:

- 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); and
- Annexes to Guideline on the Scientific Data Requirements for Plasma Master File (PMF).

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, the Council of Europe and the Australian TGA. The following details need to be provided:

(i) Collection centres
- 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).

(ii) 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.

(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 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).

(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, anti-HCV by NAT and other test parameters as recommended by US FDA or an equivalent authority. The following details need to be provided:

(i) Screening tests for markers of infection:

- List of tests performed on individual donations;
- Licence number of each test kit used;
- Validation of these screening procedure methods; and
- Details of any inventory hold/ quarantine periods and procedures.

(ii) 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.

(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 centres that have been licensed by the US FDA or equivalent authority for that purpose. The centres 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 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.

(ii) Documents that verify the fractionator/manufacturer and donation centre(s)/ organisation responsible for collecting plasma complies with PIC/S GMP and procedures; and

(iii) 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.

(d) 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:

(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 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.

(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.

1.1.2 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.

1.1.3 Manufacturing Process and Control

Data requirements for plasma-derived therapeutic 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*.
- *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)

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:

(a) Documents that verify all steps in the manufacture of the final product are conducted in establishments licensed by the US FDA or equivalent authority for that purpose. All handling and processing techniques employed should conform with the current relevant international GMP guidelines of the US FDA, the Australian TGA, the EMA CHMP or WHO.

(b) Documents verifying that each batch of source material intended for manufacture has been tested for Hepatitis B surface antigen, antibody to HIV-1&2 and antibody to Hepatitis C Virus by tests approved for such use by the US FDA 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:

(i) Plasma pooling

- Information on the number of individual plasma units pooled together;
- List of tests performed on these plasma pools; and
- Licence 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 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:

(i) 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, 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

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

(ii) 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).

(iii) 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 $60 \pm 0.5^{o}C$.
  - 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.

1.2 Body of Data – Drug Product

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

(a) Product testing

(i) Specifications and analytical methods used for release testing and expiration dating to assure product identity, purity, strength or potency and lot-to-lot consistency;

(ii) Validation protocol and results for non-compendial analytical systems to demonstrate system suitability;

(iii) 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

(iv) 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

(i) A description of the container and closure system with information on its compatibility with the biological substance; and

(ii) Evidence of container and closure integrity.

(c) Stability

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

(ii) A description of the storage conditions, study protocols and results supporting the stability of the product and any intermediates that are stored;

(iii) An expiration date supported by the results of the stability study; and

(iv) 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

(v) 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).

2 REGULATORY DECISION

When approved for registration, the product registration issued for a human plasma-derived therapeutic 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 10 years from the date of importation and be made available for inspection or upon request by HSA.

3 PMF LIFE CYCLE MANAGEMENT

Applicants are responsible for keeping the PMF updated. The updates are to be submitted annually. The annual update does not require submission via PRISM – the update should be sent to the Therapeutic Products Branch of HSA with reference to the assigned PMF number.

If a new PMF is submitted in support of a currently-registered drug product, the inclusion should be filed as an MIV-1 application – refer to B17 'Addition or Replacement of New Plasma Master File (PMF) to registered human plasma-derived product' of Appendix 14 for further details.

If a currently-registered PMF contains an update or amendment, the product registrant is responsible for updating HSA accordingly:

(a) 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

(b) 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.

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

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