APPENDIX 4

GUIDELINE ON REGISTRATION OF BIOLOGICS

IMPORTANT NOTES:

This document shall be read in conjunction with the relevant sections of the main guidance document: **Drug Registration Guidance Document (DRGD)**, which is in accordance to the legal requirements of the **Sale of Drugs Act 1952** and the **Control of Drugs and Cosmetics Regulations 1984**.

Where appropriate, the relevant WHO, EMA and ICH guidelines on biologics/ biopharmaceuticals shall be consulted.

- WHO *(https://www.who.int /)*
- EMA *(http://www.ema.europa.eu)*
- ICH *(http://www.ich.org)*

Every biologic is regulated as a new product and also considered 'high risk'. Both drug substance and drug product production must comply to Good Manufacturing Practice strictly. Adoption of GMP as an essential tool of Quality Assurance System.

The requirements for registration of biologics/ biopharmaceuticals shall be in accordance to the **ASEAN Common Technical Dossier (ACTD)** format and in adherence to the general regulatory requirement as described in sections of the main DRGD. It covers:

- Administrative information
- Product quality data
- Product safety data
- Clinical data, demonstrating clinical efficacy and capacity to meet therapeutic claims, through clinical studies

Animal derived materials/ products are commonly used in the manufacture of biologics/ biopharmaceuticals. A detailed information regarding the rationale for use of such material e.g. the source, etc. shall be provided, as per **Checklist A** and **Checklist B**; and also provide a confirmation on the presence/ absence of the animal materials in the final product through Deoxyribonucleic Acid (DNA) testing by Polymerase Chain Reaction (PCR) or any qualified and validated analytical method.

If the analytical results are positive or DNA test on the final product is not submitted, labels should contain the information of the animal origin (specifying the name of the animal(s)) accordingly.

Reference: NPRA.600-1/9/12(20): *Keperluan Ujian Deoxyribonucleic Acid (DNA) Ke Atas Produk Akhir Bagi Produk Biologik Yang Menggunakan Bahan Bersumberkan Haiwan Dalam Proses Pengilangan Produk* (24 May 2023)

This document is intended to provide guidance for the registration of biologics. However, this document will serve as a living document that will be updated/ revised further in line with the progress in scientific knowledge and experience.

Note: This document is not intended to apply to the control of genetically-modified live organisms designed to be used directly in humans, e.g. live vaccines.

Outline:

1. GENERAL INFORMATION

1.1 DEFINITIONS

i) Biopharmaceutical/ Biotechnology Product
ii) Biologic/ Biological Product

The term 'biopharmaceutical' was coined in the 80's to define proteins that were made by recombinant DNA technology [which includes hybridoma technology for monoclonal antibody (mAb) production].

Biologic/ Biological product refers to a product whose active substance is made by or derived from a living organism (plant, human, animal or microorganism) and may be produced by biotechnology methods and other cutting-edge technologies. This product imitates natural biological substances in our bodies such as hormones, enzymes or antibodies.

Biological substance is defined as a substance that is produced by or extracted from a biological source and that needs, for its characterization and the determination of its quality, a combination of physicochemical-biological testing together with the production process and its controls.

Biopharmaceuticals/ Biologics/ Biological products can also be defined as:
"A protein (including antibodies) or nucleic acid-based pharmaceuticals used for therapeutic, which is produced by means other than direct extraction from a native (non-engineered) biological source". This corresponds to the new biotechnology view (that is, by elimination, it is largely restricted to recombinant/ genetically engineered and mAb-based products).

The term 'Biotechnology product' and 'Biological product' are used to broadly refer to all biopharmaceuticals (by the broad biotechnology view).

Note:
Today, biologics have become inextricably intertwined with biopharmaceuticals, to the point where they are synonymous. The general consensus is that a 'Biologic' and 'Biopharmaceutical' are interchangeable terminology, but a biologic might incorporate some other products (e.g. allergenics, somatic cells etc.).

Biologics <u>include</u> a wide range of products such as:

1. Vaccines;
2. Blood products;
3. Monoclonal antibodies (therapeutics);
4. Recombinant proteins:
    - Insulins
    - Hormones
    - Erythropoetins and other hematopoietic factors
    - Cytokines: interferons, interleukins, colony-stimulating factors, tumour necrosis factors

5. Cell and Gene Therapy Products (CGTPs)

But do <u>not include</u>:

1. Metabolites from microorganisms; e.g. antibiotics and some hormones.
2. Macromolecules produced by chemical synthesis; e.g. peptides/ oligonucleotides produced by chemical synthesis.
3. Whole blood or cellular blood components.

Unlike small-molecule generic drugs, exact copies of biologics are impossible to produce because these are large and highly complex molecules produced in living cells. A 'biosimilar' medicinal product (a short designation for 'similar biological medicinal product') is considered as a new biological medicinal product developed to be similar in terms of quality, safety and efficacy to an already registered, well established, medicinal product. For details, please refer to Guidance Document and Guidelines for Registration of Biosimilars in Malaysia.

Cell and Gene Therapy Products (CGTPs) are regulated as Biologic products. Unlike biotechnology products which are mostly purified proteins of cells, CGTPs contain living and functional cells. Therefore, CGTP is regulated under a separate framework.

For details, please refer to Guidance Document and Guidelines for Registration of Cell and Gene Therapy (CGTPs) in Malaysia. This document provides information for manufacturers, applicants, healthcare professionals and the public on legal arrangements in Malaysia for the registration of CGTPs. The implementation of the guideline will be compulsory on 1 January 2021 as stated in Directive No. 6, 2017. Please also refer to Directive No. 19, 2020 regarding the details of mechanism for registration and enforcement of CGTPs in stages.

References:

i) Directive No. 19, 2020. *NPRA.600-1/9/13(10) Direktif Berkenaan Pelaksanaan Pendaftaran Produk dan Penguatkuasaan Secara Berperingkat Bagi Produk Terapi Sel dan Gen (CGTPs) Serta Tambahan Senarai Produk Di Luar Skop Kawalan CGTPs Oleh PBKD* (14 December 2020)

ii) Directive No. 6, 2017. *BPFK/PPP/07/25(11) Jld.1 Direktif Untuk Menguatkuasakan Penggunaan* Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products (CGTPs), December 2015 dan Good Tissue Practice Guideline, 2nd Edition, December 2015 (29 May 2017)

iii) Good Tissue Practice Guideline, 2nd Edition, December 2015

1.2 INTRODUCTION

It is acknowledged that biological substances used in the practice of medicines make a vital contribution to health care. Nevertheless, because of their nature, biologicals demand special attention with regard to their regulations to assure quality, efficacy and safety.

Biologicals are inherently variable due to their biological nature, produced from biological materials, and often tested in biological test systems, themselves variable, a feature that has important consequences for the safety and efficacy of the resulting product. Each product must be evaluated on its own merits. A prerequisite for the use of biological is therefore to assure the consistency of quality and safety from lot-to-lot.

Today, the biological field is one of enormous expansion and increasing diversity, most especially in the area of new biotechnologies. The revolution of DNA-based and other cell technologies has opened up a new and exciting vista, and in many instances, traditional products are being replaced by equivalents derived by recombinant DNA technologies or other cutting-edge technologies.

It is important to note that the demonstration that a product consistently possesses a desired characteristics of safety and efficacy will depend on a multifaceted approach on the part of manufacturer and the regulatory authority - drawing on thorough characterization of starting materials, demonstration of consistency of production, and appropriate selection of lot release tests - all under the stringent and documented controls imposed by good manufacturing practices - as well as rigorous post marketing surveillance activities.

2. SPECIFIC REQUIREMENTS FOR REGISTRATION OF BIOLOGICS

2.1 REQUIREMENTS FOR REGISTRATION OF VACCINES AND BIOTECHNOLOGY PRODUCTS

2.1.1 Vaccines:

(i) Definition of Vaccine

A vaccine contains an active component (the antigen). A vaccine is an immunogen, the administration of which is intended to stimulate the immune system to result in the prevention, amelioration or therapy of any disease or infection.

Vaccines for human use include one or more of the following:

a) microorganisms inactivated by chemical/ physical means that retain appropriate immunogenic properties;
b) living microrganisms that have been selected for their attenuation whilst retaining immunogenic properties;
c) antigen extracted from microorganisms, secreted by them or produced by recombinant DNA technology; or
d) antigen produced by chemical synthesis *in vitro*.

The antigens may be in their native state, truncated or modified following introduction of mutations, detoxified by chemical or physical means and/or aggregated, polymerized or conjugated to a carrier to increase immunogenicity. Antigens may be presented plain or in conjunction with an adjuvant, or in combination with other antigens, additives and other excipients.

(ii) Requirements for Registration of Vaccines (Chemistry, Manufacturing and Controls [CMC])

A.	**DESCRIPTION**
	▪ Description - Information on the source materials: source materials include any component/ unformulated active substance used in the manufacture of the product (e.g microorganisms, cells/ cell subtrate, immunogen) including their specifications and the tests used to demonstrate compliance with the specifications. For combination vaccines, each active substance, which will be pooled, combined with other antigens and formulated, shall be described. ▪ Any chemical modification or conjugation of the drug substance shall be described in detail. ▪ List of inactive substances, which may be present in the drug substance.
B.	**METHOD OF MANUFACTURE/ PRODUCTION**
1.	**Manufacturing Formula:** ▪ List of all materials (culture media, buffers, resins for peptide synthesis, chemicals, columns etc.) and their tests and specifications, or reference to pharmacopoeia. ▪ Complete formula inclusive of any adjuvants, diluents, preservatives, additives, stabilisers etc. ▪ Production of each antigen in the vaccine (i.e. fermenter or culture volumes for each bulk batch size as applicable and typical bulk volumes per production run). ▪ Batch formula for each batch size and final formulated bulk product. ▪ Lot numbering system for intermediates and final product.
2.	**Manufacturing Process:** **Flow Charts/ Diagrams be Accompanied by a Descriptive Narrative:** ▪ Detailed description of manufacturing process and characterization of the product. Include complete history and characterization/ characteristics of each species, strain, cell banking systems - Master Cell bank (MCB) and Working Cell Bank (WCB), cell/ seed lot system, cell substrate system, animal sources (including fertilized avian eggs), virus source or cellular sources. **Reference:** WHO TRS 878 (1998) *Annex 1: Requirements for the use of animal cells as in vitro substrates for the production of biologicals.* ▪ The flow chart should show the steps in production and a complete list of the in-process controls and tests performed on the product at each step. ▪ In-process holding steps, with time and temperature limits indicated. ▪ Description of the manufacturing processes (flow diagram) in detail to support the consistency of manufacture of drug substance - cell growth and harvesting. ▪ Identification of any processes or tests performed by contract manufacturers or testers.

	▪ Animal cells: Cells of animal origin may harbour adventitious agents and consequently pose a potentially greater risk to humans. Description of measures taken to remove, inactivate, or prevent contamination of the product from any adventitous agent present. ▪ Information on measures to prevent any catastrophic events that could render the cell banks unusable and to ensure continuous production of vaccines is crucial. For recombinant vaccines: description of the construction and characterization of the recombinant vector as well as source of master cell bank/ constructs.
3.	**Process Validation Program:** ▪ Describe general policy for process validation and provide process validation activities performed.
4.	**Handling, Storage and Packaging:** ▪ All arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage.
C.	**QUALITY CONTROL**
1.	**Starting Materials:** ▪ List of all control tests performed on raw materials, with appropriate characterisation on starting materials. ▪ List of raw materials meeting compendia specifications. ▪ List of raw materials meeting in-house specifications including the tests performed and specifications ▪ Biological starting materials (human or animal origin) with information on the requirements to avoid risk of transmissible spongiform encephlopathies (TSEs) and human diseases (HIV, hepatitis,etc) in the final product including Certificate of Suitability (CEP). *Please refer Checklist A & B* **Reference:** WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical products (2010).
2.	**Intermediate Products (as appropriate):** ▪ List the routine tests performed and specifications for intermediates.
3.	**Finished Products (including diluents):** ▪ List routine tests performed and specifications for final product. ▪ Description of the method and retest criteria.
4.	**Analytical Validation Activities Performed:** ▪ Include complete description of the protocol used for each bioassay, the control standards, the validation of inherent variability of test and the establishment of acceptance limits for each assay.

D.	**STABILITY** *(http://www.who.int/biologicals/publications/trs/areas/vaccines/stability/en/)*
	▪ Information on stability of intermediates and final product, quality control methods and rationale for the choice of tests for determining stability. ▪ Information on the dates of manufacture of the lots, the lot numbers, the vial and dose size, and the scale of production. ▪ Describe the policy for assigning the date of manufacture of each component as well as the final product (e.g combination vaccine) and diluents, as appropriate. ▪ In addition to final product stability data at the recommended storage temperature, the accelerated stability data at elevated temperatures should be sufficient to justify the choice of Vaccine Vial Monitor (VVM) for use with the product [Vaccine Vial Monitor WHO/PQS/E06/IN05.1]
E.	**LOT SUMMARY PROTOCOL AND LOT RELEASE FOR VACCINE**
	▪ Lot Summary Protocol - a document which describes the key steps and critical test results at each step of the production process must be submitted. ▪ Lot release is a basic principle in the control of vaccine. The aim of lot release is the confirmation of consistency of production as each lot of vaccine is unique. ▪ Submit Lot/ Batch Release Certificate issued by the competent authority. ▪ Every batch of registered vaccines and plasma products imported is required to undergo physical testing for Lot Release activity. ▪ COVID-19 vaccine products imported and used during a pandemic are excluded from the requirement to conduct physical testing for Lot Release activity. ▪ Lot Release activity is implemented for biological products manufactured in Malaysia. **References:** - Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities World Health Organization 2010 - Directive No. 16, 2014. *Bil. (23) dlm.BPFK/PPP/07/25 Direktif Untuk Pelaksanaan Vaccine Lot Release ke atas Semua Produk Vaksin Berdaftar di Malaysia* (14 January 2015) - Guidance Document for Biological Products Lot Release in Malaysia - Directive No. 9, 2020. *Bil. (9)dlm.BPFK/PPP/07/25Jld.4 Direktif Keperluan Menjalankan Ujian Fizikal Untuk Aktiviti Lot Release Bagi Semua Vaksin dan Produk Plasma Berdaftar Yang Diimport* (12 May 2020) - *Keputusan Pihak Berkuasa Kawalan Dadah (PBKD) Berkenaan Pengecualian Daripada Keperluan Menjalankan Ujian Fizikal Untuk Aktiviti Lot Release Bagi Semua Produk Vaksin COVID-19 Berdaftar Yang Diimport dan Digunakan Semasa Situasi Pandemik, NPRA.600-1/9/7(41)* (19 February 2021) - Directive No. 13, 2021. *NPRA.600-1/9/13(23) Direktif Berkenaan Pelaksanaan Aktiviti Lot Release Ke Atas Produk Vaksin dan Produk Plasma Yang Dikilangkan Di Malaysia* (28 April 2021)

F.	**NONCLINICAL STUDIES FOR VACCINE**
	▪ Vaccines are a diverse class of biological products and their nonclinical testing programs will depend on product-specific features and clinical indications. ▪ Preclinical testing is a prerequisite to moving a candidate vaccine from the laboratory to the clinic and includes all aspects of testing, product charaterization, proof of concept/ immunogenicity studies and safety testing in animals conducted prior to clinical testing in humans. ▪ Some live attenuated vaccines must be tested for safety in animals before they are used in humans. **References:** - WHO TRS 927 (2005) Annex 1: WHO guidelines on nonclinical evaluation of vaccines - WHO TRS 987 (2014), Annex 2: Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines
G.	**CLINICAL STUDIES FOR VACCINE**
	▪ Clinical studies designed and conducted to meet WHO and international GCP principles. ▪ Tabulated summary of the clinical development program of the vaccine, in which critical parameters that may have changed during the clinical development. ▪ Copies of publications about these trials should accompany the submission. ▪ Clinical summary: Provide detailed summary and intepretation of the safety and efficacy data obtained from clinical studies that supports the current prescribing information. ▪ Clinical Expert Report: Provide an independent clinical expert report on the clinical studies (evidence of expertise and independence should be provided) **References:** - WHO TRS 924 (2004) Annex 1: WHO guidelines on clinical evaluation of vaccines:Regulatory expectations. - WHO TRS 850 (1995) Annex 3: Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products.
H.	**POST MARKETING SURVEILLANCE FOR VACCINES**
	▪ Provide an outline of the post marketing pharmacovigilance plan for the vaccine. ▪ Periodic Benefit-Risk Evaluation Report (PBRER) in accordance to ICH Guideline E2C(R2) Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. ▪ In the case of vaccines that have recently been registered/ licensed, provide information on any ongoing phase IV studies or on any active monitoring of the safety profile that is taking place including adverse events following immunization(AEFI). ▪ Risk management plan. Please also refer to Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021.

2.1.2 Biotechnology Products

(i) Definition

Biotechnological products includes the use of the new genetic tools of recombinant DNA to make new genetically modified organisms or genetic engineering products.

Products of recombinant technology are produced by genetic modification in which DNA coding for the required product is introduced, usually by means of a plasmid or viral vector into a suitable microorganism or cell line, in which DNA is expressed and translated into protein. The desired product is then recovered by extraction and purification.

(ii) Additional Requirements for Registration of Biotechnology Products

I.	**PRODUCTION PROCESSES**
	▪ The production system shall be well defined and documented. ▪ The effectiveness of the overall purification process for active substance shall be demonstrated. ▪ Validation of procedures for removing contaminating cellular DNA, viruses and impurities.
J.	**HOST CELL AND GENE CONSTRUCT**
	▪ Source of host cells, characterisation, stability, purity and selection. ▪ Information on gene construct, amino acid sequence, vector information and genetic markers for characterisation of production cells. ▪ Cloning process to form the final gene construct and mapping of sited used in constructions of final recombinant gene construct. ▪ Method of gene construct amplication and selection of recombinant cell.
K.	**SPECIFICATIONS**
	▪ Drug substances should include assays for identity, purity, potency, physiochemical and stability. ▪ Identity and quantity of impurities along with analytical data which supports impurities profile ▪ Acceptable limits of impurities and should be included in the specifications if present in finished products.

L.	**CHARACTERISATION**
	▪ Analytical testing performed to characterise the drug substance with respect to identity, purity, potency, and stability. ▪ Characterisation of drug substance include physiochemical characterisation, immunological properties and biological activity. ▪ Sufficient sequence information to characterise the product should be obtained. ▪ Post translational modifications should be identified and adequetly characterised, especially when such modifications are likely to differ from those found in natural counterpart and may influence biological, pharmacological and immunological properties of the product.
M.	**NONCLINICAL STUDIES**
	▪ Preclinical testing is a prerequisite to moving a candidate biotechnology products from the laboratory to the clinic and includes all aspects of testing, product charaterization, proof of concept/ immunogenicity studies and safety testing in animals conducted prior to clinical testing in humans. ▪ The primary goals of nonclinical studies/preclinical safety evaluation are to identify an initial safe dose and subsequent dose escalation schemes in humans, potential target organs for toxicity (whether such toxicity is reversible) and safety parameters for clinical monitoring **Reference**: ICH Topic S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.
N.	**CLINICAL STUDIES**
	▪ Clinical studies designed and conducted to meet WHO and international GCP principles. ▪ Overall approach to the clinical developement of a medicinal product. ▪ Overview of the clinical findings and provide an evaluation of benefits and risks based upon the conclusions of the relevant clinical studies. ▪ Interpretation of how the efficacy and safety findings support the proposed dose and target indication.

O.	POST MARKETING SURVEILLANCE FOR BIOTECHNOLOGY PRODUCT
	▪ Provide an outline of the post marketing pharmacovigilance plan. ▪ Periodic Benefit-Risk Evaluation Report (PBRER) in accordance to ICH Guideline E2C(R2) Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. ▪ All relevant clinical and nonclinical safety data should cover the period of the report with exception of updates of regulatory authority or product registration holder (PRH) actions taken for safety reasons, as well as data on serious, unlisted adverse drug reactions (ADRs), which should be cumulative. ▪ Risk management plan

2.1.3 References for Vaccines and Biotechnology Products

Vaccines:

WHO (*https://extranet.who.int/pqweb/vaccines/who-technical-report-series*)
WHO Technical Report Series: Vaccines

Biotechnology Products:

WHO

i) WHO Technical Report Series 1991 No. 814, Annex 3. Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology. *(under revision)*
ii) WHO Technical Report Series 1992 No 822, Annex 3. Guidelines for assuring the quality of monoclonal antibodies for use in humans.
iii) WHO Technical Report Series No 878, Annex 1 and Addendum. Requirements for the use of animal cells as in vitro substrates for the production of biologicals.
iv) WHO Technical Report Series No.786, Annex 3. Requirements for human interferons prepared from lymphoblastoid cells (Requirements for biological substances N0.42)
v) WHO Technical Report Series No.771, Annex 7 Requirements for human interferons made by recombinant DNA techniques (Requirement for biological substance No. 41)

EMA

i) EMA/CHMP/BWP/532517/2008. Guideline on Development, Production, Characterisation and Specification for Monoclonal Antibodies and Related Products
ii) CPMP/BWP/328/99. Development Pharmaceutics for Biotechnological and Biological Products - Annex to Note for Guidance on Development Pharmaceutics.
iii) EMEA/410/01 Rev. 3 Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

ICH

i) ICH Topic Q5A (R1) Quality of Biotechnological Products: Viral Safety Evaluation Of Biotechnology Products Derived From Cell Lines Of Human Or Animal Origin.

ii) ICH Topic Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines Used for Production of r-DNA derived Protein Products.

iii) ICH Topic Q5D Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates used for Production of Biotechnological/ Biological Products.

iv) ICH Topic Q5C Quality of Biotechnological products: Stability Testing of Biotechnological/ Biological Products.

v) ICH Topic Q5D Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/ Biological Products.

vi) ICH Topic Q5E Biotechnological/ Biological Products Subject to Changes in Their Manufacturing Process: Comparability of Biotechnological/ Biological Products.

vii) ICH Topic Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products.

viii) ICH Topic Q2 (R1) Validation of Analytical Procedures: Text and Methodology.

ix) ICH Topic Q8 (R2) Pharmaceutical Development.

x) ICH Topic Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/ Biological Entities).

xi) ICH Topic S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

2.2 REQUIREMENTS FOR REGISTRATION OF BLOOD PRODUCTS

2.2.1 Definition of Blood Product

Any therapeutic product derived from human blood or plasma and produced by a manufacturing process that pools multiple units.

Plasma-derived therapies and their recombinant analogs are unique among pharmaceuticals and biologics. Their production begins with a biological starting material, human plasma. Each therapy has a unique biochemical profile as a result of differences in production and processing methods that can lead to differing clinical responses and efficacy among patients.

Hence, from the starting material, through manufacturing and final distribution to patients, the complexities of producing blood products places it in a unique class of biologics.

Blood products are regulated as medicinal product. Blood products are inherently variable due to their biological nature, and the biological methods to test them. They are subjected to comprehensive assessment of the quality, efficacy and safety.

Four (4) principal complementary approaches are adopted:

- **Starting material:** Assurance of the quality and safety of the plasma for fractionation.
- **Manufacturing technique:** Control of the fractionation and subsequent manufacturing procedures for isolation, purification, viral inactivation and/or removal steps.
- **Good manufacturing practice (GMP):** Strict adherence to GMP. Adoption of GMP as an essential tool of Quality Assurance System.
- **Product Compliance:** Standardization of biological methods needed in characterisation of in-process and finished products.

Plasma for fractionation and blood products that are regulated by NPRA includes:

- Plasma products derived from plasma collected and fractionated in Malaysia for use in Malaysia;
- Plasma products derived from plasma collected and fractionated overseas for use in Malaysia; and
- Plasma products derived from overseas-sourced plasma fractionated in Malaysia for use overseas.

Note: *This document is applicable to all plasma-derived products containing an active and inactive ingredient that is derived from human blood.*

2.2.2 Requirements for Registration of Blood Products

1.	QUALITY OF PLASMA SOURCE MATERIAL

Plasma Master File (PMF). It can also be a stand-alone document. Document pertaining to the collection and controls of source materials. Key elements of PMF are:

- Requirements for a formal contract governing purchase and supply of plasma.
- Source plasma.
- GMP status of the blood establishments/ collection centers.
- Description of the quality assurance system applying to plasma supply and use.
- Arrangements for donor selection, selection/exclusion criteria.
- Data on population epidemiology and blood-borne infections.
- Requirements for testing of samples of donations and pools. Mandatory serology on all plasma donations. Each unit of source material tested for HBsAg, anti-HIV and anti-HCV
- Plasma bags, plasma quality and plasma specifications.
- Arrangement for communication and review of post-donation information.
- Plasma inventory hold.
- Traceability from donor to end product and *vice versa.*

References:

- CHMP/BWP/3794/03 Rev. 1 Guideline on the Scientific Data Requirements for a Plasma Master File (PMF)
- Checklist of Plasma Master File for Blood Products.

2.	MANUFACTURING PROCESS AND CONTROL

Documents that verify each batch of source material intended for manufacture has been serological tested for hepatitis B (HBV), hepatitis C (HCV) and HIV. Each batch of source material must also be tested for HCV RNA by Nucleic Acid Testing (NAT) and (increasingly for other viruses including HIV, HBV, B19, and HAV) and exclusion of reactive donations.

Characterization: Physicochemical and biological characterization: Specific tests that will provide information regarding identity, purity, potency, stability and consistency of manufacture for the drug substance.

Manufacture and Controls:

i) Formula:

- Include a list of all starting materials, reagents, monoclonal antibodies, intermediate products and auxiliary materials (buffers, sera, antibiotics etc.) with specifications or statement of quality for each.
- Excipients: List of excipients.
- For non-compendial excipients: Describe tests and specifications.

	▪ For novel excipients: Include description for preparation, characterisation and controls. ▪ When used as excipient in the product, the expiry date of the plasma-derived product should not be earlier than that of the finished product. **ii) Manufacturing:** ▪ Detailed description of manufacturing process and controls to demonstrate proper quality control or prevention of possible contamination with adventitious agents. ▪ In-process and final controls. - Viral inactivation and/ or removal processes - Viral validation studies and report - Pathogen safety document inclusive of Transmissible Spongiform Encephalopathies (TSEs) risk assessment - Information or certification supporting the freedom of reagents, inactive ingredients of human or animal origin from adventitious agents. - Process consistency - Analytical validation studies - Process validation studies (purification, sterility etc.) - Batch record and batch release specifications
3.	**THE FINAL PRODUCT**
	▪ Finished product testing and quality control ▪ Stability study program and expiration date ▪ Product history ▪ Container closure system, storage and handling ▪ Package insert and labels ▪ Lot/ batch release protocols ▪ Certificate of batch review and release from a competent authority
4.	**CLINICAL STUDIES**
	▪ Demonstrating product's efficacy
5.	**POST MARKETING SURVEILLANCE – mandatory follow-up**
	▪ Periodic Benefit-Risk Evaluation Report (PBRER) Risk Management Plans

2.2.3 Checklist of Plasma Master File for Blood Products

Section	Documents	Yes/No
1.	**General Information**	
1.1	Plasma Derived Products' List	
1.2	Overall Safety Strategy • Collection of plasma • Testing • Storage	
1.3	General Logistics • Flowchart of supply chain of plasma	
2.	**Technical Information on Starting Materials/Plasma**	
2.1	Plasma Origin • Information on Collection Centers • Information on Testing Centers • Selection/ Exclusion Criteria for Donors • Traceability	
2.2	Plasma Quality and Safety • Compliance with Ph. Eur. Monographs or relevant monographs • Screening Tests for Markers of Infection • Technical Characteristics of Bags and Bottles for Blood and Plasma Collection, Including Information on Anticoagulant Solutions Used • Storage and Transport • Procedures for any Inventory Hold Period • Characterisation of the Fractionation Pool	
2.3	Contract Between Manufacturer and Blood Collection Establishment(s) • System in place between the manufacturer and/or plasma fractionators/ processor on one hand, and blood collection establishments on the other hand which defines the conditions of their interaction and their agreed specifications	

2.2.4 References for Blood Products

The National Pharmaceutical Regulatory Division's requirements for registration of blood products are aligned with the scientific guidelines and recommendations for quality, clinical efficacy and safety and non-clinical of the World Health Organization (WHO), European Medicines Agency and International Conference of Harmonization (ICH).

Where appropriate, the relevant WHO, EMA and ICH guidelines on blood products shall be consulted in particular the followings:

WHO (*https://www.who.int/health-topics/blood-products-*)

i) WHO Technical report Series 941, Annex 4, Recommendations for production, control and regulation of human plasma for fractionation.
ii) WHO Technical report Series 924, Annex 4, Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human plasma products.
iii) WHO Guidelines on tissue infectivity distribution in Transmissible Spongiform Encephalopathies.

EMA *(http://www.ema.europa.eu)*

i) EMA/CHMP/BWP/706271/2010 Committee for medicinal products for human use (CHMP) Guideline on plasma-derived medicinal products
ii) CHMP/BWP/3794/03 Rev. 1 Guideline on the Scientific Data Requirements for Plasma Master File (PMF)
iii) CPMP/BWP/268/95 Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses
iv) EMEA/410/01 Rev. 3 Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products
v) EMA/CHMP/BPWP/144533/2009 rev. 2 Guideline on the Clinical Investigation of Recombinant and Human Plasma-Derived Factor VIII Products
vi) EMA/CHMP/BPWP/144552/2009 Rev. 1, Corr. 1* Guideline on Clinical Investigation of Recombinant And Human Plasma-Derived Factor IX Products
vii) EMA/CHMP/BPWP/94033/2007 rev. 2 Guideline on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg)

ICH (*http://www.ich.org*)

i) ICH Topic 5QC Quality of Biotechnological products: Stability Testing of Biotechnological/ Biological Products.

2.3 STABILITY DATA REQUIREMENTS

2.3.1 Stability Data of Drug Substance

The submitted stability data should be from batches manufactured at the drug substance manufacturing site proposed for registration in Malaysia. At the time of submission of the new product application, the stability data requirements are as follows:

Study condition	Minimum time period covered by data during submission	Number of batches required
Long term	12 months	At least 3 commercial scale batches or representative* of the manufacturing scale of production.
Accelerated	6 months	

** Representative data: Representative of the quality of batches used in pre-clinical and clinical studies; Representative manufacturing process and storage conditions; Representative containers - ICH Q5C*

Where multiple drug substance manufacturers are proposed for registration, drug substance stability data of at least 6 months for 3 batches from each of the other sites are required, unless otherwise justified. Full real time data covering the proposed drug substance shelf life from one of the drug substance manufacturing site intended to be registered in Malaysia should be available. Where full real time data is not available from each drug substance manufacturing site to support the proposed drug substance shelf life, it may be acceptable to extrapolate the stability data from other sites if comparability can be demonstrated (Refer ICH Q5E).

2.3.2 Stability Data of Drug Product

The submitted stability data should be from batches manufactured at the drug product manufacturing site proposed for registration in Malaysia. At the time of submission of the new product application, the stability data requirements are as follows:

Study condition	Minimum time period covered by data during submission	Number of batches required
Long term	12 months	At least 3 commercial scale batches or representative* of the manufacturing scale of production.
Accelerated	6 months	

** Representative data: Representative of the quality of batches used in pre-clinical and clinical studies; Representative manufacturing process and storage conditions; Representative containers - ICH Q5C*

Where multiple drug product manufacturers are proposed for registration, drug product stability data of at least 6 months for 3 batches from each of the other sites are required, unless otherwise justified. Full real time data covering the proposed drug product shelf life from one of the drug product manufacturing site intended to be registered in Malaysia should be available. Where full real time data is not available from each drug product manufacturing site to support the proposed drug product shelf life, it may be acceptable to extrapolate the stability data from other sites if comparability can be demonstrated (Refer ICH Q5E).

Drug product stability in the case of multiple drug substance manufacturers

Where possible, batches of the drug product should be manufactured using different batches of drug substance including different drug substance manufacturers intended to be registered. If multiple drug substance manufacturers are proposed for the drug product, a commitment to conduct drug product stability studies for 1 production batch using the drug substance from each drug substance manufacturer that is not represented in the drug product stability batches is required.

3. CHECKLISTS

3.1 CHECKLIST A

Products Containing Animal-Derived Materials **WITH** a valid TSE risk evaluation Certificate of Suitability (CEP)

No.	Documents	Yes/ No
1.	TSE Risk Evaluation Certificate of Suitability (CEP)	
2.	Basic information providing a brief description of the following:	
3.	Rationale for using animal-derived materials	
4.	Source of Animals • Declaration of materials of porcine origin • Declaration of materials of other animal origin	
5.	Declaration of the nature of the animal tissue/ parts of animal used.	
6.	Description of the tissue/ organ-collection procedures and measures in place to avoid cross-contamination.	
7.	Nature and quantity of each animal-derived material used: • As a drug substance. • As an excipient or adjuvant. • As a starting material used in the manufacture of a drug substance. • As a starting material used in the manufacture of excipient. • As a reagent or culture media component used in manufacture. • As a reagent or culture media component used in establishing master cell banks. • As a reagent or culture media component used in establishing working cell banks. • Others, please provide details.	
8.	Declaration that the final product does not contain any animal-containing materials with the relevant evidence (if applicable).	
9.	Other supporting documents e.g. *Halal* Certification of the animal derived ingredient from a competent *Halal* Certification Authority.	
10.	Labelling of the animal derived materials.	

3.2 CHECKLIST B

Products Containing Animal-Derived Materials **WITHOUT** a valid TSE risk evaluation Certificate of Suitability (CEP)

Section	Documents	Yes/ No
1.	Detailed Assessment Report for the risk of TSE. The scope of this assessment report should include the following:	
2.	Rationale for using animal-derived materials	
3.	Source of Animals • Declaration of materials of porcine origin • Declaration of materials of other animal origin	
4.	Declaration of the nature of the animal tissue/ parts used.	
5.	Description of the tissue/ organ-collection procedures and measure in place to avoid cross-contamination.	
6.	Detail of the risk factors associated with the route of administration and maximum therapeutic dosage of the product.	
7.	Nature and quantity of each animal-derived material used: • As a drug substance • As an excipient or adjuvant • As a starting material used in the manufacture of a drug substance. • As a starting material used in the manufacture of excipient. • As a reagent or culture media component used in manufacture. • As a reagent or culture media component used in establishing master cell banks. • As a reagent or culture media component used in establishing working cell banks. • Others, please provide details.	
8.	Relevant information to support the claim that the manufacturing process is capable of inactivating TSE agents.	
9.	Certificates of analysis for each animal-derived materials used.	
10.	Declaration that the final product does not contain any animal-containing materials with the relevant evidence (if applicable)	
11.	Other supporting documents e.g. Halal Certification of the animal derived ingredient from a competent Halal Certification Authority.	
12.	Labelling of the animal derived materials.	