Biological Products Registration Guideline

Version 1.0

IMPORTANT NOTES: This document should be read in conjunction with the relevant sections of the main guidance document of eCTD guideline ver.3 to prepare a valid eCTD submission.

Table of Contents

Abbreviations and Acronyms:

CEP: Certificate of Suitability

CGTPs: Cell and Gene Therapy Products

CTD: Common Technical Document

DGPA&DC: Directorate General of Pharmaceutical Affairs & Drug Control

eCTD: Electronic Common Technical Document

EMA: European Medicine Agency

GVP: Good Pharmacovigilance Practice

ICH: International Conference on Harmonization

MCB: Master cell bank

MOH: Ministry of Health

PSMF: Pharmacovigilance System Master File

PTMs: Post-translational modifications

TSEs: Transmissible spongiform encephalopathies

WCB: Working cell bank

WHO: World Health Organization

Glossary:

Vaccines: a biological preparation that provides active acquired immunity to a particular infectious disease. It contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins.

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 microorganisms 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.

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.

Monoclonal antibodies: are laboratory-produced molecules engineered to serve as substitute antibodies that can restore, enhance, modify or mimic the immune system's attack on cells that aren't wanted, such as cancer cells.

Biotechnology Product (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.

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 and will not be included in this guideline.

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.

This guidance is intended to provide assistance with the submission of regulatory information of module 3 for biologics/ biopharmaceuticals products in electronic Common Technical Document format (eCTD) to the Directorate General of Pharmaceutical Affairs & Drug Control (MOH-DGPA&DC).

The requirements for registration of biologics/ biopharmaceuticals 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 (EMA) and International Conference of Harmonization (ICH).

It should be noted that the MOH-DGPA&DC has the right to request any additional information and data in order to assess adequately the safety, efficacy and quality of the medicinal products. The MOH-DGPA&DC is committed to ensuring that such requests are justifiable and decisions are clearly documented.

The requirements for registration of biologics/ biopharmaceuticals shall be in accordance to the electronic Common Technical Document (eCTD) format and in adherence to the general regulatory requirement as described in sections of the main eCTD dossiers, which covers:

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

Scope:

The scope of this guidance is to provide detailed information on how to submit the requirements for registration of biologics/ biopharmaceuticals as eCTD applications to cover specifically module 3 related documents. The hierarchal structure of this eCTD submission follows that of the CTD. All modules must be submitted electronically along with specific documents in Module 3 that is mentioned in this guideline.

Biopharmaceuticals/Biologicals:

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.

Biologics include a wide range of products such as:

1. **Vaccines**;

Please note that for the registration requirement for vaccines, refer to the Vaccine specific WHO Technical Report Series (TRS).

2. **Blood products**;

For additional registration requirement of plasma-derived medicinal products, refer to Annexure (2).

3. **Monoclonal antibodies** (therapeutics);

4. **Recombinant proteins**: - Insulins - Hormones - Erythropoietin's and other hematopoietic factors - Cytokines: interferons, interleukins, colony-stimulating factors, tumor necrosis factors

5. **Cell and Gene Therapy Products** (CGTPs)

<u>But do 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.

Please refer to the Table 1 & 2 for general M3 requirements.

Biosimilar:

A company may choose to develop a new biological medicinal product claimed to be similar (Biosimilar products) in terms of Quality, Safety and Efficacy to a reference medicinal product (RMP), which has been granted a marketing authorization on the basis of a complete dossier. The development of a biosimilar product relies in part on the scientific knowledge gained from the reference medicinal product (RMP), provided that the active substance of the biosimilar has been demonstrated to be similar, in physicochemical and biological terms, to the active substance of the reference medicinal product (RMP).

Biosimilar products are manufactured and controlled according to their own development, using state-of-the-art approaches and taking into account relevant and up-to-date information.

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product.

Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established.

Generally, the concept of biosimilarity is applicable to any biological medicinal product. However, in practice, the success of developing a biosimilar will depend on the ability to produce a medicinal product which is similar to the reference medicinal product, and to convincingly demonstrate the similar nature of the concerned products. This includes comprehensive physicochemical and biological characterization and comparison requires knowledge on how to interpret any differences between a biosimilar and its reference medicinal product.

For additional registration requirement of Biosimilar, refer to Annexure (1).

Drug Substance: Module (3)

Table (1)

3.2.S.1 General Information

3.2.S.1.1 Nomenclature	Information on Recommended International Nonproprietary Name (INN); Compendial name if relevant; Chemical name(s), Company or laboratory code
3.2.S.1.2 Structure	Brief description of active substance structure or content including the followings:
	• Molecular weight/ mass • Glycosylated /non glycosylated • Primary structure (In case of monoclonal antibody; Amino acid sequence of light chain and heavy chain should be mentioned)/ • Product variant /Heterogeneity • High order structure
3.2.S.1.3 General Properties	The details of the Characterization which includes the determination of physicochemical properties, biological activity and immunochemical properties of the drug substance by appropriate techniques should be stated. 1. **Physicochemical***:* A physicochemical characterization program will generally include a determination of the composition, physical properties, and primary structure of the desired product. 2. **Biological:** it is the biological activity that describes the specific ability or capacity of a product to achieve a defined biological effect. Examples of procedures used to measure biological activity include: Animal-based biological assays, Cell culture-based biological assays, Biochemical assays. *3.* **Immunological:** When an antibody is the desired product, its immunological properties should be fully characterized.
3.2.S.2.1 Manufacturer(s) • **Name & address of API manufacturer**	The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.
3.2.S.2.2 Description of Process and Process Controls	• A flow diagram of all manufacturing process including (upstream and downstream process) and their description. • Quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g., temperature, pressure, pH, time). • Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified.

	• A description of the manufacturing process including information on cell bank and cell culture, harvest(s), purification and modification reaction including filling storage and shipping conditions should be provided. The in-process controls for each step or stage of the process should be indicated. √ Cell culture The following information should be provided: • Flow diagram from working cell bank (WCB) through harvest. • Information for each stage should be provided (population doublings, cell concentrations, volumes, pH, cultivation time, temperature) and transfers between steps. • Description of each step including any media, materials or additives used for both cell growth and for induction. • Information with respect to operating parameters for each stage with links to section 3.2.S.2.4 (in-process controls) or specifications. √ **Purification** The following information should be provided: • Flow diagram from crude harvest, extraction and purification to final step of obtaining final active substance. • Information for each stage should be provided (pH, conductivity, processing times, hold times, elution profiles, fraction (selection) including viral inactivation step(s). • In-process controls, including acceptance criteria, should be described in detail and should be validated. Special attention should be given to the removal of viruses, nucleic acid, host cell proteins and impurities considered to pose a risk of immunogenicity. • Particular attention should be given to demonstrating the removal and/or inactivation of possible contaminating viruses and residual DNA from products manufactured using continuous cell lines. • Description of each step including scale (columns, membranes), lifetime usage for resins/membranes, regeneration, buffers used, and transfer between steps.
3.2.S.2.3 Control of Materials	• Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. • Information on the quality and control of these materials should be provided. • Biological raw materials or reagents may require careful evaluation to establish the presence or absence of deleterious endogenous or adventitious agents.
3.2.S.2.4 Control of Critical Steps and Intermediates	• Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided. • Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.
Under section *3.2.S.2.2 or 3.2.S.2.3 or 3.2.S.2.4* additional information should be provided	• Host cell line: ☐ Origin of cell line ☐ Source ☐ Cell strain

	☐ Vector (plasmid): An explanation of the source and function of the component parts of the vector, such as the origins of replication, promoters, or antibiotic markers, should be provided in addition to a restriction-enzyme map indicating at least those sites used in construction. ☐ Clone selection ☐ Cell culture media
Under section *3.2.S.2.2 or 3.2.S.2.3 or 3.2.S.2.4* additional information should be provided	• Cell bank system (MCB) Information on the cell banking system; quality control activities and cell line stability during production and storage (including procedures used to generate the Master and Working Cell Bank(s) should be provided in detail. In addition, information about the cell bank origin and storage condition, details of life expectancy and any new working cell bank should be fully characterized.
	• Characterization and control of the host cell & cell bank system (MCB) including: ☐ Genetic and phenotypic stability ☐ Cell viability ☐ Absence of adventitious agent ☐ Absence of endogenous and exogenous viruses.
3.2.S.2.5 Process Validation and/or Evaluation	• Process validation and/or evaluation studies for aseptic processing and sterilization should be included.
3.2.S.2.6 Manufacturing Process Development	• A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot, and, if available, production scale batches
3.2.S.3.1 Elucidation of Structure and Other Characteristics	Confirmation of Physicochemical Characteristics: Elucidation of product structure, including primary structure, post-translational modifications (PTMs), and higher-order structure. Confirmation of Biological Characteristics: Studies assessing binding and biological activity Preparation of Stress Materials for Characterization: Materials and methods used to prepare stress samples

3.2.S.3.2 Impurities List of Potential Impurities.	The details of purity profile of the drug substance that is assessed by a combination of analytical procedures should be provided including: ☐ **Product-related impurities which** are molecular variants arising during manufacture and/or storage, which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety. The accurate detection of degradation changes that may result from deamidation, oxidation, sulfoxidation, aggregation or fragmentation during storage should be included. ☐ **Process-related impurities** encompass those that are derived from the manufacturing process, i.e., cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., inducers, antibiotics, or media components), or downstream processing. ☐ Contaminants include all adventitiously introduced materials not intended to be part of the manufacturing process, such as chemical and biochemical materials (e.g., microbial proteases), and/or microbial species. (e.g., endotoxins, bioburden, mycoplasma, and adventitious viruses). ☐ Elemental impurities include elements which are added during cell culture processing and purification steps.
3.2.S.4 Control of Drug Substance	
3.2.S.4.1 Specifications **3.2.S.4.5 Justification of Specification**	The following tests and their acceptance criteria should be listed where appropriate: ☐ Appearance and description ☐Identity ☐ Purity and impurities ☐ Potency ☐ Quantity Justification for the active substance specification should be provided.
3.2.S.4.2 Analytical Procedures The analytical procedure used for testing the active substance should be provided in sufficient detail to enable reproducible testing by another laboratory	
3.2.S.4.3 Validation of Analytical Procedures	Analytical validation information, including experimental data for the analytical procedure used for testing the drug substance should be provided. Typical validation characteristics to be considered are selectivity, precision (repeatability, intermediate precision and reproducibility), accuracy, linearity, range, limit of quantitation, limit of detection, robustness, and system suitability.
3.2.S.4.4 Batch Analyses	Description of batches and results of three batch analyses should be provided. Results should be presented for three commercial batches against acceptance criteria
3.2.S.5 Reference Standards or Materials .	• Information on the reference standards or reference materials used for testing of the drug substance should be provided. • At the time of submission, the manufacturer should have established an appropriately characterized in-house primary reference material, prepared from lot(s) representative of production and clinical materials.

	• Where an international or national standard is available and appropriate, reference materials should be calibrated against it. • Documentation of the characterization, storage conditions and formulation supportive of reference material(s) stability should also be provided.
3.2.S.6 Container/Closure Systems	• A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate. • For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided. • The suitability should be discussed with respect to, from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching materials of construction.
3.2.S.7 Stability	
3.2.S.7.1 Stability Summary and Conclusions	A minimum of six months' stability data at the time of submission should be submitted in cases where storage periods greater than six months are requested. For drug substances with storage periods of less than six months, the minimum amount of stability data in the initial submission should be determined on a case-by-case basis.
3.2.S.7.2 Post-approval Stability Protocol and Commitment	Should be submitted for active substance
3.2.S.7.3 Stability Data	Stability studies should include: Storage conditions i.e temperature and relative humidity for accelerated and stress conditions.

Drug Product:

Table (2)

3.2.P.1 Description and Composition of the Drug Product	• The information provided should include, for example: • Description of the dosage form. • Composition, i.e., list of all components of the dosage form, and their amount on a per unit basis (including overages, if any) the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications) • Description of accompanying reconstitution diluent(s) • Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applic*able*.
3.2.P. Pharmaceutical Development	
3.2.P.2.1 Components of the Drug Product	
3.2.P.2.1.1Drug substance	• The compatibility of the drug substance with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g., water content, solubility, and particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product should be discussed. For combination products, the compatibility of drug substances with each other should be discussed.
3.2.P.2.1Excipients	• The choice of excipients listed in 3.2.P.1, their concentration, and their characteristics that can influence the drug product performance should be discussed relative to their respective functions.
3.2.P.2.2Drug Product	
3.2.P.2.2.1 Formulation Development(O)	• A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. composition) described in 3.2.P.1 should be discussed.
3.2.P.2.2.2 Overages	• Any overages in the formulation(s) described in 3.2.P.1 should be justified.
3.2.P.2.2.3 Physiochemical and Biological Properties	• Parameters relevant to the performance of the drug product, such as pH, ionic strength, dissolution, re-dispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed.
3.2.P.2.3 Manufacturing Process Development	• The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified. Differences between the manufacturing processes (es) used to produce pivotal clinical batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.
co3.2.P.2.4 Container Closure System	• The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including

	sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product).
3.2.P.2.5 Microbiological Attributes	• Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed
3.2.P.2.6 Compatibility(O)	• The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g., precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling.
3.2.P.3 Manufacture	
3.2.P.3.1 Manufacturer(s)	• The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.
3.2.P.3.2 Batch Formula	• A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.
3.2.P.3.3 Description of Manufacturing Process and Process Controls	• A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product control are conducted should be identified.
3.2.P.3.4 Controls of Critical Steps and Intermediates	• Critical Steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled. Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.
3.2.P.3.5 Process Validation and/or Evaluation	• Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilization process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2.A.2, if necessary
3.2.P.4 Control of Excipients	
3.2.P.4.1 Specifications	Information on the specifications for all the excipients employed in the formulation should be provided. List of raw materials meeting in-house specifications including the tests performed and specifications of biological starting materials (human or animal origin) with information on the requirements to avoid risk of transmissible spongiform encephalopathies (TSEs) and human diseases (HIV, hepatitis, etc) in the final product including Certificate of Suitability (CEP) should be included. Description of reference of the analytical methods used to control all the excipients employed in the formulation should be submitted. Justification for the proposed specifications of the excipients should be provided.
3.2.P.4.2 Analytical Procedures	
3.2.P.4.3 Validation of Analytical Procedures	
3.2.P.4.4 Justification of Specifications	
3.2.P.4.5 Excipients of Human or Animal Origin	• For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data).
3.2.P.4.6 Novel Excipients	• For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format.
3.2.P.5 Control of Drug Product	

3.2.P.5.1 Specifications 3.2.P.5.6Justification of Specifications	For any comments listed in the table below. The following parameters should be considered for all biological drug products: 1. Appearance and description 2. Identity 3. Purity and impurities 4. Potency 5. Protein Quantity 6. General physical test (pH, osmolality) 7. Additional test based on dosage form (liquid or solid) To justify each chosen criteria used in the specification above.
3.2.P.5.2 Analytical Procedures	Detailed information on the analytical procedures used for quality control of the drug product should be provided.
3.2.P.5.3 Validation of Analytical Procedures	Information on the validation of the analytical procedures for the drug product, including experimental data should be provided. This information should 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.
3.2.P.5.4 Batch Analyses	Provide certificates of analysis and analytical results for at least three consecutive batches signed by authorized personnel
3.2.P.5.5 Characterization of Impurities	Details on the characterization and/or determination of impurities, as applicable, depending on the nature of active substance and method used to manufacture the Biotherapeutics product should be provided.
3.2.P.6 Reference Standards or Materials	• Information on the reference standards or reference materials used for testing of the drug product should be provided, if not previously provided in "3.2.S.5 Reference Standards or Materials".
3.2.P.7 Container Closure System	• A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included where appropriate. For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided. Suitability information should be located in 3.2.P.2 • When a delivery device is presented as part of the drug product (e.g. prefilled syringe, single-use autoinjector), it is important to demonstrate the functionality of such a combination, such as the reproducibility and accuracy of the dispensed dose under testing conditions which should simulate the use of the drug product as closely as possible. • For multi-use containers such as vials or cartridges for a pen injector, proper in-use stability studies should be performed to evaluate the impact of the in-use period of the vial or the assembled device on the formulation and the functionality of the pen injector. • Dose accuracy should be demonstrated for the first and last dose delivered.

	• In addition, the effect of multiple injections/withdrawals on the closure system should be demonstrated.
3.2.P.8 Stability	
3.2.P.8.1 Stability Summary and Conclusions	• Stability study report including the study protocol, specifications, and analytical methods, detailed description of the container closure system for the product evaluated, storage conditions (temperature and relative humidity) and results for at least three lots of drug product prepared from different lots of drug substances should be provided and the reports should contain conclusions as well as proposed validity period. • A minimum of twelve months' data at the time of submission should be provided in cases where storage periods greater than six months are requested, unless otherwise justified. • For storage periods of less than six months, the stability data should cover the whole proposed shelf life. • Stability studies under accelerated and stress conditions, including the impact of the container closure system, should also be provided. • The stability program may be selected on the basis of a matrix system and/or by bracketing. The manufacturer should state the stability program design. • In liquid products (other than sealed ampoules), stability studies should include samples maintained in the inverted or horizontal position (i.e., in contact with the closure), as well as in the upright position, to determine the effects of the closure on product quality.
3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitments	Include the stability program or stability commitment to be carried out once the drug product is on the market, including the number of batches to be included in the study each year and the tests to be performed. These results should be submitted periodically to update the information on the stability of the drug product.
3.2.P.8.3 Stability Data	Evidence should be provided to demonstrate that the product is stable for the proposed validity period under the indicated storage conditions. Stability data submitted should be for at least three batches and include the following: 1) Information on stability of drug product, quality control methods for determining stability. 2) Information on the dates of manufacture of the lots, the lot numbers, the vial and dose size, and the scale of production. 3) For lyophilized products the data supporting the shelf-life of the product following reconstitution should be included. If the drug product is frozen, data supporting the stability of the product through a stated number of freeze-thaw cycles should be provided.

Annexure 1:

Additional Requirements for Biosimilar Drugs Registration

Purpose and Scope

The purpose of this document describes the special considerations for registration of biosimilar products. The applicants should also read in conjunction with the "Guidance Notes on Registration of Pharmaceutical Products/Substances" on the requirements for new biological products, where applicable. The applicants may be required to provide additional information on top of the requirements stated in the guidance notes to allow evaluation of safety, quality, and efficacy of the products applying for registration.

General Requirements

- Biosimilar product must be proven to be similar to a registered originator product (i.e. reference product) in terms of safety and efficacy. The applicant must provide evidence to support all aspects of the application, starting with characterization and evaluation of quality attributes followed by non-clinical and clinical studies of the product. Comprehensive characterization and comparison at the quality level provide the basis for possible data reduction of non-clinical and clinical studies.
- If differences between the biosimilar and reference products are found during the above characterization and comparison studies, the reasons for the differences should be explained and justified; and additional data may be required to further document the possible impact of those differences on the similarity profile.
- In order to register a biosimilar product, the applicant should submit a full quality dossier with the application that includes a complete characterization of the biosimilar product and its production and purification processes. The comparability exercise between the biosimilar and reference products in the quality part represents an additional element to the traditional full quality dossier for pharmaceutical products containing chemical or biological materials as active ingredients or substances.
- The comparability data at quality level is an additional set of data over that which is normally required for an originator product and may be presented as a separate section in the quality dossier. The comparability exercise should be completed by non-clinical and clinical studies to provide an integrated set of comparative data.

- The active substance(s) must be similar in molecular and biological terms between the biosimilar and reference products.

- The dose form, strength, and route of administration should be the same between the biosimilar and reference products.
- The proposed indication(s) of the biosimilar product must fall within the clinical indication(s) granted to the reference product in Oman.

Reference Product:

- The reference product must have been registered in Oman. In addition, a registered biosimilar product cannot be chosen as the reference product in a new application for registration as a biosimilar product.
- To support registration of the biosimilar product, similarity of the biosimilar and reference products should be demonstrated through "head-to-head" comparisons. The same reference product should be used throughout the entire comparability exercise.

Special Requirement

Quality Documents

- A full quality dossier should be submitted with information on

(i) extensive characterization studies of both the active substance and the finished product

(ii) The development, manufacturing process, and quality control of both the active substance and the finished product.

- A separate section in the quality dossier on comparability exercise between the biosimilar and reference products on both the active substances and the finished products should be submitted. Where applicable, the applicant may refer to the WHO "Guidelines on Evaluation of Similar Biotherapeutic Products" for details of the study requirements.
- It is acknowledged that the quality data of the biosimilar and reference products will not be identical and so, the applicant should provide justification(s) for any observed differences with regard to their potential impact on safety and efficacy.
- The differences of the quality data may affect the requirements for the amount of nonclinical and clinical data, and will be considered with a case-by-case approach. If sufficient similarities between the biosimilar and reference products cannot be established based on the submitted quality data, it is very likely that reduced non-clinical and clinical data will not be sufficient to confirm the similarity profile.

Annexure 2:

Additional Requirements for plasma-derived medicinal products

Introduction:

Human plasma contains many proteins which, following extraction, purification, and formulation into medicinal products are of great medical importance. The technique of plasma fractionation, devised by Cohn and colleagues, enabled the widespread use of medicinal products extracted from human plasma. The potential for viral transmission is well recognized, and because of the large number of donations which are pooled, a single contaminated batch of a plasma-derived product, with the contamination possibly originating from a single donation, can transmit viral disease to a large number of recipients. Measures taken to prevent infection include selection of donors, screening of individual donations and plasma pools for markers of infection with known viruses and validation of the production process for inactivation or removal of viruses

Purpose and Scope:

The purpose of this document describes the special considerations for registration of plasma-derived medicinal products. The applicants should also read in conjunction with the "Guidance on Plasma-Derived Medicinal Products, where applicable.

General Requirements

1. **Starting material:**

Plasma Master File (PMF)

The plasma master file is a standalone document and should be filed separately with the application. The following points need to be considered:

- The collection and testing of starting material are major factors in the quality assurance of the manufacture of biological medicinal products. Measures taken to reduce risks for transmission of blood borne infections by plasma-derived medicinal products include the meticulous control of starting material.
- The immunization of donors to obtain immunoglobulins with specific activities should comply with the requirements of the international monograph. This also includes testing of donors of erythrocytes used for immunization of donors for anti-D plasma. This information, which is specific to a particular product (e.g. immunization scheme used for specific immunoglobulins), should be included in section 3.2 S of the dossier for the relevant product and not in the PMF.

- 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). Including information about: Collection centers, Epidemiology data on

blood-borne infections, Selection/exclusion criteria -Characteristics of donation, Exclusion criteria for donors.

- Documents that verify the fractionators/manufacturer and donation centre(s)/ organization responsible for collecting plasma complies with Good Manufacturing Practices (GMP).

- **Testing of starting material**
  *****Plasma pools should be tested according to the monograph "Human plasma for fractionation". Additional testing and specifications of plasma pools are required for specific products, e.g. virus inactivated pooled plasma and anti-D immunoglobulins. These monographs require testing for HBsAg, HIV antibodies, HCV RNA of each fractionation pool and additional testing for B19V DNA for specific products (i.e. virus-inactivated pooled plasma and anti D immunoglobulins) and HAV RNA for virus-inactivated pooled plasma.

2. **Intermediates:** 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.

3. **Safety and Viral Inactivation:**

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

- 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.

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

- There are several factors can affect the safety of blood donations in transfusion medicine. The most important factor which have implications are blood borne infections and include viruses found in plasma which establish a viraemia such as HBV, HCV, HIV 1 and 2, HAV and B19V, or any other emerging infectious viruses or other agents such as vCJD. The manufacturer should have controls to this factor.

-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.

Pharmacovigilance

As for most biological medicines, data from pre-authorization clinical studies are usually too limited to identify all potential unwanted effects of Biological product . In particular, rare adverse events are unlikely to be encountered in the limited clinical trial populations being tested. In addition, a close monitoring of the clinical safety of all approved indications and a continued benefit–risk assessment is therefore necessary in the post-marketing phase.

The manufacturer should submit a safety specification and pharmacovigilance plan at the time of submission of the marketing authorization application. The safety specification should describe important identified or potential safety issues for the biological product and for the substance class and/or any that are specific for it. The pharmacovigilance plan should describe the planned post-marketing activities and methods based on the safety specification. In some cases, risk minimization measures such as educational material for patients and/or treating physicians may enhance the safety of using the biological product.

Manufacturers should ensure that, at the time of the marketing authorization, they have in place an appropriate pharmacovigilance system, including the services of a qualified person responsible for monitoring pharmacovigilance and the necessary means for notification of adverse reactions that occur in any of the countries where the product is marketed.

After the marketing authorization is granted, it is the responsibility of the DGPA&DC to monitor closely the compliance of manufacturers with their marketing commitments, where appropriate, and particularly with their pharmacovigilance obligations.

The main aim of this guideline is to provide guidance on the requirements, procedures, roles and activities in the field of PV, for marketing authorization holders (MAHs) of biological products for human use in the Sultanate of Oman. PV obligations apply to all biological products available in Oman, both registered and non-registered.

For all products registered in Oman, the relevant pharmaceutical companies/MAHs whose products are registered and marketed in Oman have to have appropriate documentations as laid down in Good Pharmacovigilance modules viz.,

1. Pharmacovigilance systems and their quality systems
2. Pharmacovigilance System Master File (PSMF)
3. Pharmacovigilance Inspections
4. Pharmacovigilance Audits
5. Risk Management Systems
6. Management and reporting adverse reactions to biological products
7. Periodic Safety Update Reports (PSURs)/ Periodic Benefit Risk Evaluation Report (PBRER)
8. Post Authorization Safety Studies
9. Signal Management
10. Safety Communication
11. Risk Minimization Measures

This information has been derived from the Guideline on Good Pharmacovigilance Practice (GVP) for Arab Countries (Version 2), International Conference for Harmonization (ICH) and the European Medicine Agency (EMA) guidelines.

Traceability

Product traceability is an important aspect in the pharmacovigilance of biological products due to their greater inherent variability when compared to chemically synthesized medicines. The main reason behind this is to easily and rapidly detect newly emerging and product specific safety concerns and immunogenicity throughout the life-cycle of the product including supply locations and patients. Pharmaceutical products, especially biologicals, should be easily traced by the batch number, which should be recorded at all levels of supply chain i.e. from manufacturer release to the patient. Such records should be readily available with a similar standard across all countries using biological and they should easily retrieved.

Risk Management System

An approved risk management plan (RMP) is considered as an essential part of any product registration. Should any changes arise after registration, the RMP must be updated and approved too.

References:

1. https://extranet.edqm.eu/publications/recherches_CEP.shtml
2. https://www.fda.gov/industry/color-additive inventories/summary-color-additives-use-united-states-foods-drugs-cosmetics-and-medical-devices#table2A
3. ICH Topic Q 5 C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
4. ICH Topic Q 6 B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Product
5. Guideline on production and quality control of monoclonal antibodies.
6. Guideline on similar biological medicinal products
7. Guidance on Plasma-Derived Medicinal Products
8. https://www.npra.gov.my/easyarticles/images/users/1047/drgd/APPENDIX-4---Guideline-on-Registration-of-Biologics.pdf
9. Guideline on Biosimilar Products (Version 1.0), SFDA.
10. Guideline on similar biological medicinal products, CHMP/437/04 Rev 1.
11. Guidelines for the production and quality control of monoclonal antibodies and related products intended for medicinal use
12. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)
13. ICH Topic Q 5 E Comparability of Biotechnological/Biological Products
14. ICH Topic Q 5 B Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines Used for Production of r-DNA Derived Protein Products
15. ICH Topic Q 5 A (R1) Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
16. Guidelines on evaluation of similar Biotherapeutics products (SBPs)