GUIDELINE FOR REGISTRATION OF BIOLOGICS FOR HUMAN USE, 2014

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REVISION HISTORY

This guideline supersedes the Data Requirement for Biologics and Biotechnology Products of Guideline for Registration of Medicinal Product 2013. However, for other categories of products, the Guideline for Registration of Medicinal Product 2013 remains valid.

ABBREVIATIONS AND ACRONYMS

cGMP:	current Good Manufacturing Practice Certificate
CoPP:	Certificate of Pharmaceutical Product
DNA:	Deoxyribonucleic Acid
NRA:	National Regulatory Authority
MAH:	Market Authorization Holder
PSUR:	Periodic Safety Update Report
DRA:	Drug Regulatory Authority
DTAC:	Drug Technical Advisory Committee
CoA:	Certificate of Analysis
ADR:	Adverse Drug Reaction
WHO:	World Health Organization
INN:	International Non-proprietary name
USP:	United States Pharmacopoeia
BP:	British Pharmacopoeia

JP:	Japanese Pharmacopoeia
API:	Active Pharmaceutical Ingredient
GCP:	Good Clinical Practices
Act:	Medicines Act of the Kingdom of Bhutan 2003
Regulation:	Bhutan Medicines Rules and Regulation 2012
Product:	Biologics and biotechnology products
Authority:	Drug Regulatory Authority
Committee:	Registration Committee for Registration of the Medicinal Products
SBP:	Systolic blood pressure
DBP:	Diastolic blood pressure
DNA:	Deoxyribonucleic acid
rDNA:	recombinant DNA
mRNA:	messenger RNA
HIV:	Human immunodeficiency virus
AIDS:	Acquired Immune Deficiency Syndrome
TTI:	Transfusion transmitted infection
ELISA:	Enzyme linked immunosorbent assay
NAT:	Nucleic acid testing
US FDA:	United States Food and Drug Administration
Ph. Eur.:	European Pharmacopoeia

DEFINITION OF THE TERMINOLOGIES USED IN THIS GUIDELINE:

1. **Adverse Drug Reaction** means any noxious, undesired, or unintended response to a drug, which occurs at therapeutic dose.

2. **Drug Technical Advisory Committee** refers to the committee appointed under section 5.1 of the Medicines Act of the Kingdom of Bhutan 2003.

3. **Evaluation** refers to the assessment of the dossier and product sample submitted by the applicant using predefined set of criteria and checklist.

4. **Full Evaluation route** refers to route of evaluation of product dossier for market authorization holder who has fulfilled the requirement of detailed documentation for product registration.

5. **Abridge Evaluation route** refers to route of evaluation of product dossier for market authorization holder who has fulfilled the requirement of abbreviated documentation for product registration.

6. **Good Manufacturing Practices** refers to a system for ensuring that products are consistently produced and controlled according to quality standards.

7. **Market authorization Holder** refers to the firm in whose name the product is registered/ licensed.

8. **Product Dossier** refers to the detailed product profile or technical documents generated from the product manufacturer for the purpose of the product registration.

9. **Committee** for product registration refers to the committee as approved by the Bhutan Medicines Board for evaluation of biologic (s).

10. **Bioactive substance** for biologics and biotechnology products refers to the active ingredient responsible for therapeutic effect of the finished product.

11. **General Document Evaluation** refers to the evaluation of Part I under data requirement of full evaluation route in the dossier.

12. **Technical Document Evaluation** refers to the evaluation of Part II, Part III and Part IV data requirements of the full evaluation and all the documents of the abridged evaluation.

13. **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.

14. **Biosimilar** refers to a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed biotherapeutic product by at least one of the referenced NRA. Biosimilars are not generic biologics/biogenerics.

15. **API (Active Pharmaceutical Ingredient, or Drug Substance)** refers to any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product by formulation with excipients and that, when used in the production of a drug, becomes an active ingredient of the drug product.
    Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.
    (ICH Q7A, http://www.fda.gov/CDER/guidance/4286fnl.htm#P1272_96843)

16. **Referenced NRA** refers to following national drug regulatory authorities which are referenced by DRA:
    i. Australia Therapeutic Goods Administration (TGA);
    ii. Health Canada (HC);
    iii. US Food and Drug Administration (FDA);
    iv. European Medicines Agency (EMA)
    v. UK Medicines and Healthcare Products Regulatory Agency (UK MHRA)
    vi. Japan DRA
    vii. Health Science Authority of Singapore (HSA)
    viii. Drug Control Authority of Malaysia (BPFK)
    ix. Thai Food and Drug Administration(FDA)

17. **Biotherapeutics** refers to therapeutic biological products, some of which are produced by recombinant DNA technology.

18. **Immunogens** means any substance or organism that provokes an immune response (produces immunity) when introduced into the body or agents that may be used to trigger the immune response, such as vaccines, or during disease, such as allergens.

19. **Cytometric analysis** refers to the characterization and measurement of cells and cellular constituents.

20. **Immunoblots** is a technique for or the blot resulting from, analyzing or identifying proteins via antigen-antibody specific reactions, as in Western blot technique.

21. **Neurovirulence testing** refers to the tendency or capacity of a microorganism to cause disease of the nervous system.

22. **Serotyping** refers to a group of organisms, microorganisms, or cells distinguished by their shared specific antigens as determined by serologic testing.

23. **Neutralization assay** refers to the assay where neutralizing antibodies inhibit biological activity of a target, and cell viability or plaque reduction is the endpoint.

24. Adventitious agent refers to acquired, accidental contaminants in a cell line, such as viruses and toxins; often infectious agents. OR coming from another source and not inherent or innate.

25. **Compendia** refer to collection of concise but detailed information about a particular subject, especially in a book or other publication.

26. **Phenotype** refers to the observable physical or biochemical characteristics of an organism, as determined by both genetic makeup and environmental influences.

27. **Genotype** refers to the genetic constitution of an organism or a group of organisms.

28. **Gene construct** is an artificially constructed segment of nucleic acid that is going to be "transplanted" into a target tissue or cell. It often contains a DNA insert, which contains the gene sequence encoding a protein of interest, that has been sub cloned into a vector, which contains bacterial resistance genes for growth in bacteria, and promoters for expression in the organism.

29. **Cell bank** is a storage facility for frozen tissue samples held for research purposes and for surgical reconstruction of damaged body structures.

30. **Cryopreservative** refers to the maintenance of the viability of excised tissue or organs by storing at very low temperatures.

31. **Karyology** refers to the study of cell nuclei specially with reference to the number and shape of the chromosomes

32. **rDNA** refers to genetically engineered DNA prepared by transplanting or splicing one or more segments of DNA into the chromosomes of an organism from a different species. Such DNA becomes part of the host's genetic makeup and is replicated.

33. **Bioburden** refers to the number of contaminating microorganisms on a certain amount of material before it is sterilised.

34. **Primary cells** are cells taken directly from a living organism, which is not immortalized.

35. **Derivatization** is a technique used in chemistry which transforms a chemical compound into a product of similar chemical structure, called a derivative.

36. **Tumorigenicity** refers to the extent to which a substance can cause tumor.

37. **Vaccine** refers to an immunogen, the administration of which is intended to stimulate immune system to result in the prevention, amelioration or therapy of any disease or infection. A vaccine may be a live attenuated preparation of bacteria, viruses or parasites, inactivated (killed) whole organisms, living irradiated cells, crude fractions or purified immunogens, including those derived from recombinant DNA in a host cell, conjugates formed by covalent linkage of components, synthetic antigens, polynucleotides (such as the plasmid DNA vaccines), living vectored cells expressing specific heterologous immunogens, or cells pulsed with immunogen. It may also be a combination of vaccines listed above.

38. **Local authorized dealer** refers to the pharmaceutical suppliers in the country who are certified by DRA and has valid technical authorization

39. **Epitope** refers to an antigenic determinant or a site on the surface of an antigen molecule to which an antibody attaches itself

SCOPE

In pursuant to Chapter VI section 16.2 of the Medicines Act of the Kingdom of Bhutan 2003; this guideline will apply for registration of following categories of biologics which are meant for human use in Bhutan:

1. Vaccines
2. Blood products
3. Monoclonal antibodies (therapeutics)
4. Recombinant proteins including, but not limited to Insulins, Hormones, Erythropoetins and other hematopoietic factors, Cytokines: interferons, interleukins, colony-stimulating factors and tumor necrosis factors

Out of Scope:

This guideline doesn't apply to the following products:

1. Biologics which are meant for use in veterinary sectors (use guideline for registration of biologics in veterinary sector)
2. Diagnostic agents and test kits
3. Non-medicated medical and contraceptive devices
4. Non-medicated bandages, surgical dressings, plaster, dental fillings
5. Instruments, apparatus, syringes, needles, sutures, catheters
6. Food

APPLICATION PROCEDURE

An application for registration should be made by the principal manufacturer or any other local authorized dealer.

Application for Registration

1. The application for registration of each product under abridged and full evaluation should be made in form V-PAR and form VI-PFR of the regulation respectively. These forms are attached with this guideline as annexure 1 and 2.
2. Products which are packed together with the diluents will be classified as a Combination Pack Product and should be registered as a single product.
3. Separate applications should be made in respect of different formulation of same product.
4. The applicant must ensure that the name of the manufacturer(s), address and contact details are consistent throughout application e.g in the manufacturing license, GMP certificate, CoPP, Authorization letter etc.
5. The application for registration must be accompanied by the token fees of Nu. 150 (one hundred fifty only), which may be revised from time to time along with the documents.
6. After filing the application, the dossier at DRA undergoes 2 stage evaluation viz., General Document Evaluation and Technical Document evaluation.

GENERAL REQUIREMENTS OF THE DOSSIER

The dossier should be:

1. Submitted typewritten or computer printed
2. In English or Dzongkha or both
3. Where originals are in another language, copies should be presented together with certified English translations
4. Be complete as per the specifications detailed in this guideline
5. Containing a table of contents, the flow of the information must be as per the flow of the document requirement in this guideline
6. Indexed to the various appendices
7. Numbered on every page
8. Properly bonded
9. In A4 size paper
10. Contain price structure of the biologics
11. Contain certificates or testimonies obtained from other agencies or authorities in original or in case of duplicate or electronic submission, attested by the Public Notary or a Court of Justice

DATA REQUIREMENTS

The data requirement for product registration is based on the route of evaluation that the product will be subjected to. The route is broadly classified into abridged evaluation and full evaluation. In general, the product registration will follow full evaluation route while the abridged evaluation is granted for those products wherein the safety, efficacy and quality parameters of the specific products are evaluated by the referenced NRA.

ABRIDGED REGISTRATION

Abridge evaluation should be applicable to:

1. A product that has been evaluated and approved by at least one of the referenced NRA at the time of submission of application for registration;
2. Products which are pre-qualified by WHO, OIE or other UN recognized international organizations.

Data Requirements for Abridged Registration

To consider the product under abridged evaluation route, following documents are required:

A. Documentary evidence to support abridged evaluation:

1. Official approval letters or equivalent documents (like valid registration certificate for the said product) from the referenced NRA that certify the registration status of the finished product *OR*
2. Proof of pre-qualification or approval if the product is pre-qualified

The above evidence must be provided either in original or notarized, in case of a copy.

B. Declaration Letter

Official letter declaring that all aspects of the product's quality, safety and efficacy intended for sale/distribution in Bhutan are identical as that currently approved by the referenced NRA or prequalified by international organization.

This includes, but not limited to the formulation, site(s) of manufacture, raw materials used, use of adjuvants, method of manufacture, release and shelf life specifications and primary packaging.

C. Letter of Authorization from the manufacturer

1. In case of the dealer being involved, letter of authorization issued by the manufacturer must be submitted
2. The authorization letter should include the list of products authorized by the manufacturer to the dealer
3. If the letter has provision of validity, the letter must be valid
4. If the principle manufacturer has regional office, it must be detailed in the authorization letter
5. If the invoice is to be generated from the regional office, it must be stated on the letter of authorization

D. Price Structure

The price structure should:

1. Indicate price applicable to the wholesaler, retailer and the maximum retail price.
2. Include value indicated either in USD, Indian rupee (Rs.) or local Bhutanese currency

(Nu.) per unit pack size

E. Product Sample

1. Samples of finished product submitted for registration should be taken at random from an actual production batch
2. Samples submitted must be intact and it must be in final commercial pack with original labels and package inserts
3. Product samples submitted must have a remaining shelf-life of at least 75% of the total shelf life

F. Specimen of Package, Label and insert

1. Specimen of original package, label and insert must be furnished. This specimen must be same as commercially available specimens
2. At least 3 specimens must be included in the dossier
3. Following minimum information is required:
   I. Product name
   II. Dosage form
   III. Name and strength of active ingredient(s)/ content of formulation with quantity of ingredients per dosage unit
   IV. Batch no.
   V. Manufacture date
   VI. Expiry date
   VII. Pharmacoepial standard
   VIII. Route of administration (if applicable)
   IX. Storage conditions
   X. Name and address of the manufacturer
   XI. Net content of the package
   XII. Pack sizes (unit/volume)
   XIII. Warnings/ cautions (if applicable)
   XIV. Precautionary information like "Keep medicine out of reach of children" or the words "Controlled Medicine", where applicable
   XV. Directions for handling, where applicable

4. If the product is without an outer carton, the inner label should bear all the information that is required
5. The colour of labels should be differentiated between strengths of products. The label must be made from good quality material.

G. Summary of Product Characteristics

Complete and concise summary of product particulars as would normally appear in product monographs, package inserts, immunogenic information sheets, data sheets etc must be submitted. It should include:

1. Name and dosage form of product
2. Therapeutic class
3. Description
4. Name(s) and strength(s) of active ingredient(s) (immunogenic substance)

5. Mode of action
6. Toxicology
7. Indication
8. Contraindications
9. Reconstitution
10. Dose and dosage regimen
11. Adverse Event Following Immunization (AEFI)
12. Immunogenic interactions
13. Precaution(s)/warning(s)
14. Storage condition(s)

FULL REGISTRATION

Full evaluation route is applicable to all the category of biologics which does not fulfill abridged evaluation criteria.

Data Requirements for Full Registration

The biologics which are evaluated via full evaluation are required to fulfill data requirements as given below:

Part I - General Documents
Part II - Product Profile
Part III - Quality Profile
Part IV - Pharmacological Documents

Part I - General Documents

In general following documents are required. If however, the product is manufactured in the country; certifications like manufacturing license, CoPP, Evidence of Free Sale, cGMP certificate, etc issued by the Authority may not be necessary.

A. Company profile

The company profile of the principle ***manufacturer for the finished product and API*** should include:

1. Brief description of the company with its Organization chart and its detailed address
2. Complete address of the manufacturing site if different from the organization
3. Address of the Corporate Office, phone and fax numbers
4. Name and qualification of the key personnel (Head of Quality Assurance-Quality Control, Store and Production) where possible with the signatures of the personnel against their names
5. List of the biologics manufactured
6. State whether the company is manufacturing under loan license or not. If so, details must be included

B. Current Good Manufacturing Practices (cGMP) certificate

cGMP certificate should:

1. Bear the Certificate number

2. Bear the name of the firm, the date of certification, date of expiry and identity of the issuing authority
3. Be valid and should have remaining validity of at least 6 months during the time of submission ***OR***
4. If the certificate is nearing its expiry, evidence of application or under process letter for renewal of same issued by the licensing authority must be submitted along with the certificate
5. Follow the PIC/S or WHO standard

C. Manufacturing License

Manufacturing license should:

1. Bear the license number
2. Bear the name of the firm, the date of certification, date of expiry and identity of the issuing authority
3. Be valid and should have remaining validity of at least 6 months during the time of submission ***OR***
4. If the license is nearing its expiry, evidence of application or under process letter for renewal of same issued by the licensing authority must be submitted along with the license
5. Contain the list of products applied for registration
6. Loan license and contract manufacturing status where applicable must be reflected

D. Certificate of the Pharmaceutical Product (CoPP)

CoPP should:

1. Bear the certificate number
2. Bear the date of issue, expiry date, the name of the product, name of the manufacturer and name of the issuing authority
3. Be valid and should have remaining validity of at least 6 months during the time of submission ***OR***
4. If the certificate is nearing its expiry, evidence of application or under process letter for renewal of same issued by the licensing authority must be submitted along with the certificate
5. Originate from the country where the product is being manufactured
6. Where possible, the CoPP should be in the format of the WHO Certification Scheme on the Quality of Pharmaceutical Products

E. Letter of Authorization from the manufacturer

The letter of authorization from the manufacturer should fulfill following conditions:

1. In case of the dealer being involved, letter of authorization issued by the manufacturer must be submitted
2. The authorization letter should include the list of products authorized by the manufacturer to the dealer
3. The regional office of the principle manufacturing firm may provide the authorization letter. In such case, the letter of authorization from the principal manufacturer to these offices should be submitted as well

F. Evidence of Free Sale

1. If the CoPP format is not as per the format of WHO Certification Scheme on the Quality of Pharmaceutical Products; the document indicating the free sale of the product in the country of origin must be furnished. It must be issued by the authorized authority from the country of origin. It should contain the following:
   I. Brand name
   II. Generic name or International non-proprietary
   III. Dosage form and strength
   IV. Complete name and address of manufacturer

2. The Evidence of Free Sale must be provided either in original or notarized, in case of a copy
3. If the product is manufactured only for the purpose of EXPORT, valid justification is required on why this product is not available in the country of origin

G. Price Structure

The price structure should:

1. Indicate price applicable to the wholesaler, retailer and the maximum retail price
2. Include value indicated either in USD, Indian rupee (Rs.) or local Bhutanese currency (Nu.) per unit pack size

H. Letter of Evidence

The letter of evidence stating that the information content in the dossier is originated from the principal manufacturer must be enclosed

I. Product Sample

1. Samples of finished product submitted for registration should be taken at random from an actual production batch.
2. Samples submitted must be intact and it must be in final commercial pack with original labels and package inserts.
3. Product samples submitted must have a remaining shelf-life of at least 75% of the total shelf life.

J. Specimen of Package, Label and insert

1. Specimen of original package, label and insert must be furnished. This specimen must be same as commercially available specimens
2. Atleast 3 specimens must be included in the dossier
3. Following minimum information is required:
   I. Product name
   II. Dosage form
   III. Name and strength of active ingredient(s)/ content of formulation with quantity of ingredients per dosage unit
   IV. Batch no.
   V. Manufacture date
   VI. Expiry date
   VII. Pharmacoepial standard

VIII. Route of administration (if applicable)
IX. Storage conditions
X. Name and address of the manufacturer
XI. Net content of the package
XII. Pack sizes (unit/volume)
XIII. Warnings/ cautions (if applicable)
XIV. Precautionary information like "Keep medicine out of reach of children" or the words "Controlled Medicine", where applicable
XV. Directions for handling, where applicable

4. If the product is without an outer carton, the inner label should bear all the information that is required
5. The colour of labels should be differentiated between strengths of products. The label must be made from good quality material

Part II - Product Profile

Complete and concise summary of product particulars as would normally appear in product monographs, package inserts, immunogenic information sheets, data sheets etc must be submitted. This should include following information:

I. Generic or International Non-proprietary name (INN)
II. Brand name or trade name (if applicable)
III. Dosage form
IV. Name(s) and strength(s) of active ingredient(s) (immunogenic substance)
V. Strength of the finished product
VI. Therapeutic class
VII. Mode of action
VIII. Toxicology
IX. Indication
X. Contraindications
XI. Reconstitution
XII. Dose and dosage regimen
XIII. Adverse Event Following Immunization (AEFI)
XIV. Immunogenic interactions
XV. Precaution(s)/warning(s)
XVI. Storage condition(s)
XVII. Reference of the official standards of the finished product (e.g compendial pharmacopoeias or manufacturer's in-house specification).
XVIII. List of all the ingredients in the dosage form and their amount on a per unit basis, as per the label claim and batch quantities
XIX. Description of the organoleptic characteristics of the product.
XX. Physico-chemical properties such as colour, shape, particle size, pH, solubility in water and other solvents, existence/absence of polymorphs and pseudo-polymorphs, hygroscopic nature, etc. When describing a liquids, state clearly whether it is in the form of a solution (clear), suspension, emulsion, etc
XXI. Commercial presentation of packaging and pack size in terms of quantity/weight/volume, etc.

Part III - Quality Profile

A. DRUG SUBSTANCE AS RAW MATERIALS (QUALITY, SAFETY AND NON-CLINICAL ASPECTS)

1. Composition of the product

A list of the active ingredients (immunogens) and other additives should be given and their amount per unit dose should be stated.

1.1 Description

This section should contain the following description of the immunogenic substance:

1.1.1 The **biological name** (including strain and/or clone designation) or chemical name, including any approved name.

1.1.2 The **source of the cells**, including microbes from which the immunogenic substance was derived, the active components of the cell fractions or purified antigens and the physical and chemical properties of the synthetic immunogenic substance.

1.1.3 Any **chemical modification or conjugation** of the immunogenic substance.

1.1.4 List of **any inactive substance** which may be present in the immunogenic substance.

1.1.5 For blood and blood products, plasma master file where documents that verify each donor of source material has undergone a proper screening procedure and has met all established health criteria as per *National Standards for Blood Transfusion Service 2013* should be provided.

1.2 Characterization

This section should contain a description of all analytical testing performed to characterize the immunogenic substance with respect to identity, potency and stability.

1.2.1 Test results can be presented in either tabular form, legible copies of chromatograms or spectra, photographs of gels or immunoblots, actual histograms of cytometric analysis or other appropriate formats.

1.2.2 Data should be well organized and fully indexed to enable easy access.

1.2.3 Results for quantitative assays should be presented as actual data not generally as “Pass” or “Fail”

1.2.4 Data comparing the immunogenic substance with pharmacopeia standard or referenced product should be provided.

1.3 Biological activity tests

Further characterization of vaccines may include the following tests if applicable depending on the type of vaccine:

1.3.1 Specific identity testing

1.3.2 Cytometric analysis

1.3.3 Neurovirulence testing

1.3.4 Serotyping

1.3.5 Electrophoretic typing

1.3.6 Inactivation studies

1.3.7 Neutralization assay

1.3.8 Titrations

A description and results of all relevant *in vivo* and *in vitro* biological testing (bioassays) performed on the manufacturer's reference standard lot or other relevant lots to demonstrate the potency and activity(ies) of the immunogenic substance should be provided.
A complete description of the protocol used for each bioassay, the control standard used, the validation of the inherent variability of the test and the established acceptance limits for each assay should be included. The characteristics of specific antibodies used in the immunochemical or serological assays should also be included.

2. Description of the manufacturing facility

2.1 Identification

The application should include the name(s), address(es) and other pertinent organizational information for each manufacturer responsible for any portion of the manufacture or testing operations for the immunogenic substance.

2.2 Manufacture of other products

A comprehensive list of additional products that are manufactured or manipulated in the same area(s) used to produce the immunogenic substance that is the subject to this application should be provided.
This section should include:

2.2.1 A brief description of the type and development status of the additional immunogenic substances/product

2.2.2 Indicate the areas into which these other products will be introduced, whether on an ongoing or campaign basis and what manufacturing steps will be performed in the multiple use area(s).

2.2.3 Indicate whether the manufacture of other products will utilize the same contact equipment and if so, how that equipment will be cleaned and validated between operations for the manufacturing of different products. Data should be provided for the validation and cleaning in the appropriate section.

2.3 Layout

The applicant should submit a simple flow diagram of the general layout of the facilities which traces the immunogenic substance through the manufacturing process. The diagram(s) should be sufficiently clear to enable visualization of the production flow and to identify adjacent operations that may create particular concerns.

2.4 Precautions against contamination

For all areas in which operations for the preparation of cell banks and product manufacturing are performed, including areas for the handling of animals used in production, the information concerning precautions, taken to prevent contamination or cross contamination should be provided.

3. Method of manufacture

A detailed description of the manufacturing and controls for each immunogenic substance should be provided to demonstrate proper quality control and prevention of possible contamination with adventitious agent(s).

3.1 Raw materials

A list of all materials as provided in section 4, used in the manufacture of the immunogenic substance and their tests and specifications or reference to official compendia should be provided. For purchased materials, representative certificates of analysis from the supplier(s) and/or manufacturer's acceptance criteria should be provided.

3.2 Flow charts

3.2.1 A complete visual representation of the manufacturing process flow should be provided for each immunogenic substance.

3.2.2 This flow chart should show the steps in production, equipment and materials used, area where the operation is performed and a complete list of the in-process controls and tests performed on the product at each step.

3.2.3 In-process holding steps should be included with time and temperature limits indicated.

4. Detailed description of source of raw material(s)

The following minimum information should be provided:

4.1 Natural Source

4.1.1 Animal sources

a) The species and age of animals
b) The health status of the animals e.g. specific pathogen free
c) The results of adventitious agent
d) The animal husbandry practices e.g. quarantine procedures used to ensure the suitability of the animals
e) The veterinary and laboratory monitoring used to ensure the suitability of the animals
f) A description of the inoculation of the animals and the method of harvest

4.1.2 Virus sources

a) The original source of the virus
b) The passage history of the virus strains
c) Details of the seed lot system
d) The culture techniques for virus seed maintenance

4.1.3 Cellular sources

a) Microbial cells
b) Origin of isolate
c) Species
d) Biochemistry (fermentation profile etc.)
e) Strain identifier and specific identifying characteristics (serotype etc)
f) Virulence (attenuation method, if performed)
g) Generic characterization, if known (markers, inserts, deletions, etc.)
h) Plasmids
i) Genetic stability

4.1.4 Animal cells

4.1.4.1 Primary cells

1. The species and age of the animals and source of tissue from which the cells are derived
2. The health status of the animals from which the cells are derived e.g. specific pathogen free
3. The animal husbandry practices (quarantine etc.) used to ensure the suitability of the animals
4. The veterinary and laboratory monitoring used to ensure the suitability of the animals
5. A description of the preparation of primary cell substrates
6. An explanation of the concurrent testing done to demonstrate the absence of adventitious agents and the results of those tests.

4.1.4.2 Cell lines

1. For human cell substrates:
   - 1.1 The source of cells should be clearly described including the materials and methods used, the tissue or organ of origin, ethnic and geographical origin, age, gender and general physiological condition of the donor.
   - 1.2 The health or media history of the donor, if known should be provided along with the results of any tests for pathogenic agents.

2. For animal cell lines:
   - 2.1 The source of cells should be clearly described including species, strains, breeding conditions, tissue or organ of origin, geographical origin, age, sex and general physiological condition of the donor.
   - 2.2 Testing for detection of adventitious agents should be undertaken with consideration of the possible agents which may be present in the cells. Results of all tests should be included.

4.1.4.3 DNA Recombinant Products

For recombinant DNA (rDNA) derived products and rDNA-modified cell substrates, detailed information should be provided regarding the host cells and the source and function of the component parts of the recombinant gene construct.

i. Host cells

A description of the source, relevant phenotype, and genotype should be provided for the host cell used to construct the biological production system. The results of the characterization of the host cell for phenotypic and genotypic markers including those that will be monitored for cell stability, purity and selection should be included.

ii. Gene construct

A detailed description of the gene, which was introduced into, the host cells, including both the cell type and origin of the source material should be provided. A description of the method(s) used to prepare the gene construct and a restriction enzyme digestion map of the construct should be included.

The complete nucleotide sequence of the coding region and regulatory elements of the expression construct, with translated amino acid sequence should be provided including annotation designating all important sequence features.

iii. Vector

Detailed information regarding the vector and genetic elements should be provided, including description of the source and function of the component parts of the vector e.g. origins of replication, antibiotic resistance genes, promoters, enhancers. A restriction enzyme digestion map indicating at least those sites used in construction of the vector should be provided. Genetic markers critical for the characterization of the production cells should also be indicated.

iv. Final gene construct

A detailed description should be provided of the cloning process which resulted in the final recombinant gene construct. The information should include a step-by-step description of the assembly of the gene fragments and vector or other genetic elements to form the final gene construct. A restriction enzyme digestion map indicating at least those sites used in constructions of the final product construct should be provided.

v. Cloning and establishment of the recombinant cell lines

Depending on the methods to be utilized to transfer a final gene construct or isolated gene fragments into its host, the mechanism of transfer, copy number, and the physical state of the final construct inside the host cell (i.e. integrated or extra chromosomal) should be provided. In addition, the amplification of the gene construct, if applicable, selection of the recombinant cell clone and establishment of the seed should be completely described.

4.1.4.4 Cell Bank System

A description of the cell banking procedures used should be provided including:

1. The banking system used
2. The size of the cell banks
3. The container and closure system used
4. A detailed description of the methods, reagents and media used for preparation of the cell banks
5. The conditions employed for cryopreservation and storage
6. In-process control(s) and storage conditions.

A description should be provided for the procedures used to avoid microbial contamination and cross-contamination by other cell types present in the facility, and the procedures that allow the banked cells to be traced.

I. Master Cell Bank (MCB)

A complete history and characterization of the Master Cell Bank (MCB) should be provided, including, as appropriate for the given cells:

a) The biological or chemical method used to derive the cell bank
b) Biochemistry (cell surface markers, isoenzyme analysis, specific protein or mRNA, etc.)
c) Specific identifying characteristics (morphology, serotype etc.)

d) Karyology and tumorigenicity
e) Virulence markers
f) Genetic markers
g) Purity of culture
h) Media and components (e.g. serum)

II. Working Cell Bank (WCB)

This section should also contain a description of the procedures used to derive a WCB from the MCB.

a) The description should include the identification system used for the WCB as well as the procedures for storage and cataloging of the WCB.
b) The assays used for qualification and characterization of each new WCB should be included with the results of those assays for the WCB currently in use.
c) If applicable, a description of animal passage of the WCB performed to assure the presence of virulence factors which are protective antigens should be supplied.

III. End of Production Cells (EPC)

a) For r-DNA derived immunogenic substances, provide a detailed description of the characterization of the EPC that demonstrates that the biological production system is consistent during growth.
b) Include the results of the analysis of the EPC for phenotypic or genotypic markers to confirm identity and purity.
c) This section should also contain the results of test supporting the freedom of the EPC from contamination by adventitious agents.
d) Submit the results of restriction enzyme analysis of the gene constructs in the EPC.
e) Detailed information on the characterization and testing of banked cell substrates should be submitted. This should include the results of testing to confirm the identity, purity and suitability of the cell substrate for manufacturing use.

4.1.4.5 Cell Growth and Harvesting

This section should contain a description of each of the following manufacturing processes, as appropriate. The description should contain sufficient detail to support the consistency of manufacturing process.

i. Propagation

This section should contain description of:

a) Each step in propagation from retrieval of the WCB to culture harvest (stages of growth)
b) The media used at each step (including water quality) with details of their preparation and sterilization
c) The inoculation and growth of initial and sub-cultures, including volumes, time and temperatures of incubation(s)
d) How transfers are performed
e) Precautions taken to control contamination
f) In-process testing which determines inoculation of the main culture system

g) The nature of the main culture system including operating conditions and control parameters
h) The parallel control cell cultures, if applicable, including number and volume of culture vessels
i) Induction of antigen, if applicable
j) The use of antibiotics in the medium and rationale, if applicable.

ii. Harvest

A description of the method(s) used for separation of crude substance from the propagation system (precipitation, centrifugation, filtration etc.) should be provided. Brief description should be given for the following:

a) The process parameters monitored
b) The criteria for harvesting
c) The determination of yields
d) The criteria for pooling more than one harvest, if applicable.

A description of the procedures used to monitor bioburden (including acceptance limits) or sterility should be included. If the harvested crude immunogenic substance is held prior to further processing, a description of storage conditions and time limits should be provided.

4.1.5 Human source (applies only to blood and blood products)

The Plasma Master File should include information on the plasma used as starting/raw material, in particular:

4.1.5.1 Documents that verify each donor of source material has undergone a proper screening procedure and has met all established health criteria (including viral risks requirements as per the *National Standards for Bloods Transfusion Service 2013.*

4.1.5.2 Documents that verify 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. There must be no pooling of plasma for testing purposes. Details need to be provided regarding the screening tests for markers of infection:

a) List of tests performed on individual donation
b) License number for each test kit used
c) Validation of these screening methods
d) Details of any inventory hold/ quarantine periods and procedures.

4.1.5.3 Documents that verify 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 regarding system to trace the path of any donation need to be provided:

a) Confirm that there is a system in place that ensures traceability from the donation centre to finished product and *vice versa*; and,
b) Provide information on steps that would be taken if it is found retrospectively that the donation(s) should have been excluded from processing.

4.1.5.4 Documents that verify 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
   a) Information on the name of bag, manufacturer, anticoagulant solution, composition and specification
   b) Indication on conformance to a particular standard (e.g. WHO, Ph. Eur.).

ii. Plasma quality
   a) Information on storage conditions and maximum storage time with an indication on how conditions are maintained from collection centre to the manufacturer
   b) Confirmation of compliance with appropriate standard.

iii. Plasma specification
   a) Information on specification(s) and confirm compliance to specification(s); and,
   b) Information on in-process tests on the plasma pool, if any.

4.1.5.5 Documents that verify that the source materials do not contain an additive 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.

4.1.5.6 Documents that verify the fractionator/manufacturer and donation centre(s)/ organisation responsible for collecting plasma comply with PIC/S GMP and procedures. Letter of commitment from the Manufacturer stating that:
   a) All collection centres have signed the contract
   b) The national authority will be notified in the event of a serious failure of a blood collection centre.

4.1.6 Purification and Downstream Processing

This section should contain a description of the methods and materials by which intermediate forms and the final bulk of the immunogenic substance are separated and concentrated from the cells, media, solvents or solutions used in the production process. The description of each step of the purification process should also include the accompanying analytical tests developed or adopted by the manufacturer to show identity, purity and concentration and the levels of product related and non-product related impurities.

Description should be provided for:

4.1.6.1 Inactivation (if appropriate)

a) How culture purity is verified before inactivation
b) The method(s) and agent(s) used for inactivation
c) The method(s) undertaken to prevent aggregation and assure homogeneous access of inactivating agent(s)
d) The stage in production where inactivation or killing is performed and

e) The parameters which are monitored.

Verification of the adequacy and margin of safety achieved by the method of inactivation or killing should be provided.

4.1.6.2 Purification (if appropriate)

a) The methods used, including specialized equipment such as columns; ultracentrifugation and custom reagents such as monoclonal antibodies
b) The process parameters monitored
c) The determination of yields
d) In-process testing (e.g. sensitivity and specificity of ELISA)
e) The criteria for pooling more than one batch, if applicable
f) Sterility and precautions taken to prevent contamination during purification
g) The reuse and/or regeneration of columns and adsorbents and Monitoring for residual impurities and leachable reagents
h) A list of in-process controls and tests for purity, identity, and biological activity should be provided. A list of the final acceptance criteria for the purified immunogenic substance should be provided. If the purified substance is held prior to further processing, a description of the storage conditions and time limits should be included.

4.1.6.3 Stability processing

a) Provide a description with objectives and rationale for any post-purification steps performed to produce a stabilized intermediate (e.g. adsorption, addition of stabilizers, addition of preservatives, lyophilization (in bulk), desiccation, etc.)
b) A description of precautions taken to prevent contamination during these processes
c) If the stabilized intermediate is held prior to further processing, a description of storage conditions and time limits should be included.
d) Verification of the stability of the immunogenic substance under the conditions described should be provided.

4.1.6.4 Detoxification

For toxoid or toxoid-containing vaccines, the detoxification procedures should be described in detail for the toxin component(s):

a) The method(s) and agent(s) used for detoxification.
b) The stage in production where detoxification is performed.
c) The parameters which are monitored and
d) Confirmation of detoxification.

4.2 Synthetic Immunogenic Substance

For the purposes of this guidance, synthetic immunogenic substance includes; linear or complex synthetic peptides, or modified synthetic or semi-synthetic immunogens such as lipopeptides to carrier protein or polysaccharide to carrier protein conjugates.

4.2.1 Synthetic Peptides

The detail of the peptide synthesis including purification procedures should be provided.

4.2.2 Conjugates and Modified Immunogenic Substance

4.2.2.1 This section of the guidance refers to immunogenic substances derived from another immunogenic substance or intermediate through chemical or enzymatic modification, e.g. conjugation of an immunogen to a carrier molecule, enzymatic or chemical cleavage and purification of the non-toxic subunit of a toxin, or derivatization.

4.2.2.2 The modification may change the fundamental immunogenicity, toxicity, stability or pharmacokinetics of the source immunogenic substance.

4.2.2.3 The derived immunogenic substance may include linking moieties and new antigenic epitopes. (define)

4.2.3 Manufacturing procedure

This section should provide a detailed description of:

4.2.3.1 The specifications and acceptance criteria, for the native immunogenic substance, starting materials, which assure suitability for conjugation or modification

4.2.3.2 The conditions of all reactions and/or snytheses used to produce a semi-synthetic conjugated molecule, derivatized molecule, or subunit, including intermediate forms of the reactants and immunogenic substance; also include:

a) the process parameters which are monitored,
b) in-process controls,
c) test for identity and biologic activity, and
d) any post-purification steps performed to produce a stabilized derived immunogenic substance.

4.2.3.3 The application should include a description of the methods and equipment used for separation of unreacted materials and reagents from the conjugate, derivative, or subunit, and a rationale for the choice of methods.

4.2.4 Specification

4.2.4.1 Specifications should be provided for each modified immunogenic substance, including identity, purity, potency, physico-chemical properties, and stability data.

4.2.4.2 If test results for the derived substance will be reported for final release of the immunogenic product a validation report, to include estimates of variability and upper and lower limits, should be provided for each specification.

4.2.4.3 Specifications should include the amount of unreacted starting materials and process reagents unless their removal has been validated.

4.3 Batch Records

A completed representative batch record of the process of production of the immunogenic substance (equivalent to biologics) should be provided.

5. Process Controls

5.1 In-process controls

5.1.1 For all in-process tests indicated in the flow charts, a brief description of the sampling procedures and the test methods used should be provided.

5.1.2 For tests performed at significant phases of production, the criteria for accepting or rejecting an in-process batch should be specified.

5.2 Process Validation

a) A summary report, including protocols and results should be provided for the validation studies of each critical process or factor that affects immunogenic substance specifications.
b) The validation study reports with statistical rigor should document the variability in each process as it relates to final specifications and quality.

5.2.1 Propagation

5.2.1.1 A growth curve or tabular representation of growth characteristics for each propagation step, based on historical performance under specified conditions, should be provided.

5.2.1.2 Data should be included which demonstrate the efficiency of induction of antigen production, if applicable.

5.2.1.3 Data should also be provided showing the stability of genetic markers under the conditions of propagation, if applicable.

5.2.2 Harvest

5.2.2.1 For each method or combination of methods, a tabulation should be provided of yields purity, and viability (if applicable) of the crude harvest, based on historical performance.

5.2.3 Inactivation

5.2.3.1 Inactivation or killing curves, or a tabular representation, based on historical performance should be provided.

5.2.3.2 Validation of the titration method to measure residual live agents, including sensitivity in a background of inactivated agents, should be provided.

5.2.4 Purification

5.2.4.1 For each method or combination of methods used, a tabulation of yields, purity and biological activity should be provided.

5.2.4.2 Verification of the removal or dilution of product related and non-product related impurities, e.g. processing reagents, endotoxin contaminating cell proteins or nucleic acids, and other residual contaminants should be included.

5.2.4.3 A standard denominator (e.g. international units) should be used to facilitate comparison (with? through processing, concentration, or dilution.

5.2.5 Microbiology

5.2.5.1 A description and documentation of the validation studies for any processes used for media sterilization, effectiveness of preservatives, decontamination, inactivation of cells prior to their release to the environment, if such inactivation is required, etc. should be provided.

5.2.5.2 If the immunogenic substance is intended to be sterile, information should be submitted.

5.3 Control of Bioburden

5.3.1 For each process which is not intended to be sterile, documentation should be provided for the control of extraneous bioburden by a tabulation of in-process testing for bioburden.

6. Manufacturing Consistency

a) Consistency of the manufacturing process for each biological product component should be demonstrated by manufacturing at least three, preferably consecutive, batches of immunogenic substance of a size corresponding to that for routine production.
b) The establishment and use of reference standards in assuring consistency in product characteristics should be described.

6.1 Reference Standards

6.1.1 A description of the preparation, characterization, and stability of primary and working reference standards should be provided.
6.1.2 A detailed description of the procedures to qualify new lots of reference standards and acceptance criteria for a new reference standard should be included.

6.2 Release Test

6.2.1 Release (acceptance criteria) test results and other (for information only) characterization data (e.g. certificates of analysis) for each batch should be submitted.

7. Immunogenic Substance Specifications

7.1 Specifications

7.1.1 This section should contain the specifications and tests for each immunogenic substance. These should include assays for identity, purity, potency (biologic effect), physicochemical properties which predict potency, and where applicable, stability data.
7.1.2 For highly purified substances, purity in reference to the theoretical composition should be presented.
7.1.3 In some cases test results for the stabilized intermediates of component antigens should be included in the final release of the immunogenic product.
7.1.4 The results of the validation studies for each of these specifications, including estimates of variability and upper and lower limits should be provided.

7.2 Impurities Profile

This section should include a discussion of the impurities in the immunogenic substance. The identity and quantity of impurities should be provided along with the analytical data (gels, elution profiles, Western blots etc.) which support the impurities profile. Impurities that should be characterized and quantified include:

7.2.1 Product related impurities (variants or alterations of antigen occurring during processing or storage)
7.2.2 Process related impurities
7.2.3 Media components
7.2.4 Cell substrate proteins or nucleic acids or

7.2.5 Process reagents which have not been removed by the purification process

8. Reprocessing

This section should include detailed information on any reprocessing that may be done on each immunogenic substance. The information provided for each reprocessing procedure should include:

8.1 A description of the conditions or criteria, determined from process controls or specifications, which indicate the need for re-processing
8.2 A description of the reprocessing step
8.3 The Standard Operating Procedure for the step
8.4 A description of any additional or modified in-process controls or specifications which are included to monitor re-processing steps
8.5 A description of the modifications in batch numbers and documentation of re-processing in the Batch Production Record (BPR) and
8.6 The evidence derived from validation studies which assures that product identity, purity, potency and stability is preserved for re-processed batches.

9. Container and Closure System

A description of the container and closure system, and its compatibility with the immunogenic substance should be submitted.

9.1 The submission should include detailed information concerning the supplier, address and the results of compatibility, toxicity and biological tests.
9.2 If the immunogenic substance is intended to be sterile, evidence of container and closure integrity for the duration of the proposed expiry period should be provided.

10. Immunogenic Substance Stability

This section should contain information on the stability of the immunogenic substance and any in-process material at each holding step.

B. MANUFACTURING PROCESS, QUALITY, SAFETY, EFFICACY AND NON-CLINICAL ASPECTS OF THE BIOLOGICS

1. Manufacturing process

1.1 General Considerations

1.1.1 Manufacturers must prepare and submit two [DRA's discretion] copies of details on production process. It must cite internationally accepted regulatory requirements such as that of the World Health Organization. Once approved and stamped as satisfactory, one copy of each will be retained with the DRA, and one copy will be returned to the manufacturer.
1.1.2 The manufacturer presenting the product must provide a flow chart indicating the source(s) of all raw materials, antigens and /or other components.
1.1.3 The manufacturer is responsible for ensuring that all relevant and up-to-date OP and SO are received by the DRA.

1.2 Production outline

A detailed document describing manufacturing methods and testing procedures should be submitted. The production outline should include the following information:

1.2.1 Micro-organism, source, isolation and passage history, strains present and proportion of each strain, genetic characterization if the product is biotechnology-derived;

1.2.2 Culture conditions, composition of media and storage conditions;

1.2.3 Technique for harvesting the micro-organism;

1.2.4 Description of assembly of serial; Data on the finished product tests and testing criteria for purity, potency, safety and efficacy;

1.2.5 Label recommendations (use, route of administration and dosage) and precaution statements.

1.2.6 A confidentiality statement to protect business information should also be provided

1.3 Manufacturing process

1.3.1 Manufacture of Biologics should be controlled according to its own process development taking into account state-of-the-art information on manufacturing processes and consequences on product characteristics. Therefore there should be adequate data on the following:

1.3.1.1 The development and documentation for biologics should cover two distinct but complementary aspects such as:

a) molecular characteristics and quality attributes (QA) of the target product profile should be comparable to the reference medicinal product

b) performance and consistency of the manufacturing process should be validated

1.3.2 The quality target product profile (QTPP) of biosimilars should be based on data collected on the chosen reference medicinal product, including publicly available information and data obtained from extensive characterization of the reference medicinal product. The QTPP should be detailed at an early stage of development and forms the basis for the development of the biosimilar product and its manufacturing process.

1.3.3 Potential risks introduced by the proposed manufacturing process, as compared to the reference medicinal product if any during the development of a biosimilar should be clearly stated.

For instance,

1.3.3.1 The use of novel expression system should be carefully considered, as they may introduce additional risk such as atypical glycosylation pattern higher variability or even a different impurity profile compared to the reference medicinal product.

1.3.3.2 The active substance may introduce its own molecular variants, isoforms or other product related substances as well as process related impurities.

1.3.3.3 The applicant should take into account the state-of-the-art technology, regardless of the formulation selected, the suitability of the proposed formulation with regards to stability, compatibility (i.e. interaction with excipients, diluents and packaging materials), integrity, activity and strength of the active substance should be demonstrated.

1.3.3.4 If a different formulation and/or container/closure system to the reference medicinal product is selected (including any material that is in contact with the medicinal product), its potential impact on the safety and efficacy should be appropriately justified.

1.4 Summary Test Results

Manufacturers must submit summary test results to verify uniformity, and serial-to-serial consistency of production serials. These data demonstrate the manufacturer's ability to consistently manufacture serials that meet OP specifications.

1.5 Supporting Data

Data must be provided to support the purity, potency, safety and efficacy of the product and to support label claims.

Studies supporting efficacy and safety must be conducted with serials equivalent to the final product described in the submitted OP.

All reports must be dated and signed by the study investigator and by the quality assurance personnel of the manufacturer. Only one copy of each supporting document is required. Copies of pertinent reprints (scientific publications) are required if these are referred to in the reports. Individual animal data for all the animals used in the studies are required; however, these data can be presented in summary tables. The use of double-sided photocopies is recommended to reduce the volume of paper submitted.

Any later amendments, including additions and corrections, to a signed and dated research report should be prepared as new, signed and dated documents detailing the changes and referencing the original report.

2. Quality

In order to endorse the manufacturer, a company profile should be provided including the following details:

a) Brief history of the company
b) Quality policy
c) List of product category manufactured
d) Authentic cGMP certificate
e) Manufacturing process with process controls

2.1 Product description and presentation with sample

The qualitative statement describing the following should be provided

2.1.1 Name and address of the company

2.1.2 The products should come in standard packaging, leak proof containers properly labeled with international nonproprietary name and commercial name

2.1.3 Labels include vial labels, cartons, package inserts and all other printed information distributed with the product. The manufacturer must supply a certified translation in English including all the information about the product.

2.1.4 Product license authorization number, batch and lot number, manufacture and expiry dates.

2.1.5 Physical state (solid, liquid, and powder), colour, clarity, concentration

2.1.6 Number of doses per final container should be clearly cited on the label expressed in the same unit as the reference product.

*A sample of the product should be availed for physical verification

2.2 Product formulation

2.2.1 A list should be provided of all the components of the product, active immunogenic substances(s) and other ingredients with unit specification and clear reasons of inclusion.

2.3 Product identity and characterization

2.3.1 An identity test should be performed on at least one of the labeled containers and verify the contents of the vials. The method used to establish the identity of the product should be described and it should include an evaluation of its target specificity.

2.4 Product brochure should contain details on

2.4.1 Product data (MSDS, abbreviations)

2.4.2 Specification such as intended target, preparation, methods and requirements for infusion

2.4.3 Process validation (literature on appropriateness of the vectors and host cells used for preparation)

2.4.4 Impurities and purity certificate of the product should be clearly stated

2.4.5 Should include comparison of affinity of the products to the intended target (dose-response curve and other studies carried out on the products/using the products for reference)

2.5 Shipment/ delivery

2.5.1 As a DRA prequalification scheme, manufacturers are expected to ensure that their packaging complies with the criteria specified for the specified product.

2.5.2 Any changes introduced in the packaging or the shipment procedures must be documented and evidence of validation produced.

2.5.3 Temperature monitoring electronic devices should be included in all shipments to monitor temperature during the entire shipment process

2.5.4 Temperatures within the insulated container should be monitored using sensors and should remain within the tolerance of +/- 1^{0}C

2.6 Reference product validation:

2.6.1 Several different batches of the reference biologics with the relative age should be considered when establishing a quality profile.

2.6.2 Comparable safety and efficacy should be demonstrated. Any minor deviation in quality attributes of the product from the reference material should be substantiated with proper safety and efficacy study.

2.7 Sterility:

2.7.1 It is mandatory for each product should be tested for bacterial, viral and mycotic contaminations as per the method approved by the cGMP.

2.7.2 The company should produce data for repeated sterility tests performed on the products.

2.8 Purity and impurities:

2.8.1 Process-related impurities (e.g host cell proteins, host cell DNA, reagents and downstream impurities) may differ from process to process. However the acceptable limits and the potential risks of the identified impurities should be justified and documented.

2.9 Storage/ Stability/Expiry date

Maintenance of biological activity is generally dependent on the maintaining molecular conformation which is further dependent on temperature, oxidizing agents, exposure to light, ionic content, freeze/thaw and shear. Product-specific analytical approaches for the validation of the product stability should be demonstrated.

2.9.1 Primary data to support storage period and condition for the product should be based on long-term, real-time, and real-condition stability studies, and these should be further supported by accelerated- and stress-condition stability data, as available, to justify the claimed shelf-life.

2.9.2 A detailed protocol for the assessment and results of the stability testing throughout its shelf life should be provided. The expiry date should be defined on the basis of shelf life supported by the stability studies.

2.9.3 Stability studies should include an evaluation of the impact of the container closure system on the formulated product throughout the shelf-life on at least three batches for which manufacture and storage is representative of the commercial process.

2.9.4 Data should be supplied for all different container closure combinations that will be marketed

2.10 Quality check

For evidence of quality and reproducibility, standard testing procedure, method validation along with acceptance criterion for each product should be clearly stated

3 Safety

It is important to identify critical quality attributes that may impact the safety and efficacy of the product. Safety issues include microbiological safety (due to the use of biological materials either during the manufacturing process or as an integral part of the products), pharmacological/ biological toxicity, immunogenicity and potential tumourigenicity (e.g for growth factors, immunosuppressive monoclonal antibodies and cell therapy products).

3.1 Additional safety assays carried out on both the reference and the finished product in parallel should be stated.

3.2 Duration of follow-ups should be justified based on the treatment course with the product to measure the immune response and the disappearance of the product from the system

3.3 Reports on longtime/short term safe usages and immunogenic potency, details on bioavailability, should be stated for each product with indications for Post infusion management where applicable

3.4 Post marketing commitments from the manufacturers (willingness for product retraction and stand answerable for any product related queries)
3.5 For the extrapolation of safety, the manufacturer should consider the disease-related factors and the patient-related factors, such as different co-medication, co-morbidities and immunological status and contraindications should be submitted
3.6 Random Quality check on the supplied product would be carried out as per the approved protocol and mandates of the DRA.

4 Efficacy

The efficacy of each batch of product should be determined and should preferably reflect its desired action under ideal storage conditions. The particular approach to efficacy determination should be explained and justified.

Certificates of analysis and analytical results should include:

i. Controlled clinical trials
ii. Studies on potential beneficial interactions or potential decrease in efficacy when administered at the same with other therapeutics
iii. Studies on interchangeability with other biologics
iv. Local and systemic tolerance studies to determine the maximum tolerable dose

Efficacy study reports comparable to the reference should be stated along with the dose/exposure vs. response curves wherever possible.
To ensure precise efficacy, limiting factors that may contribute to the immunogenicity of the product should be clearly stated.

5 Non-Clinical studies

5.1 Guidelines related to the non-clinical safety evaluation of biotechnology products, represent a set of general guiding principles to be applied on a **case-by-case** basis.
5.2 It includes all in vivo and in vitro testing performed before and during the development of clinical vaccines and all aspects of product characterization, proof of immunogenicity studies, and safety testing in animals (1).
5.3 A properly designed study for non-clinical evaluation should be carried out to answer the safety concerns as described in the *table 1*.

Table 1

Area of nonclinical Evaluation	Primary concern	Scope of nonclinical evaluation
In vitro assessments		
Process development, quality control and quality assurance	Process is expected to meet cGMP standards	Process control and laboratory studies related to all steps in process to prepare the product
Product characterization	Product quality is appropriate for use in preclinical and clinical studies	Genetic, biochemical, and biological characteristics of the product
In vivo assessments		
Toxicity and safety	Product risks are	Safety indicators such as:

Testing	appropriate for anticipated uses	range of safe dose; single and repeated safe doses; safety parameters for clinical monitoring;
Immunogenicity and Efficacy	Product effects are appropriate for anticipated uses	Effect indicators such as: type of immune responses for clinical evaluation; frequency and duration of immune responses; priming and boosting parameters; protective effects in animal challenge studies

** Modified from (1)*

Requirements for Nonclinical evaluation

i. Selection of the pharmacologically or toxicologically relevant animal species (age of the animals the physiological state, the weight of the animals, etc)
ii. The manner of delivery, including relevant dose or amount, route of administration, and treatment regimen
iii. Stability of the test material under the conditions of use
iv. Interpretation of results

A wide range of pharmacological, biochemical, immunological, toxicological and histopathological investigative techniques should be used, where appropriate, to assess a product's effect over an appropriate range of doses and, in accordance with the desired clinical indication(s), during both acute and chronic exposure.

Part IV: Pharmacological documents

A. Clinical Evaluation of Vaccines

The Clinical studies should comply with the ***'World Health Organization Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations'***. *WHO Technical Report Series No. 924, 2004*, (most recent version) or other equivalent International Guideline(s).

Clinical data should adhere to the principles described in the WHO guidelines for good clinical practice for trials on pharmaceutical vaccines and all clinical trials should be approved by relevant NRA.

The following documents should be made available for the clinical assessment:

1. **Evidence of registration with the respective National Regulatory Authority and or International NRA.**

2. **Data on Phase I, II, III and IV clinical studies as described below:**

a. ***Phase I Studies***

These are intended to define the safety and reactogenicity of the vaccine and to seek preliminary information on immunogenicity. Dose and route of administration should be evaluated with respect to these parameters. Generally these studies are conducted on small groups of immunocompetent healthy adults (50 to 200) who present low risk of being infected by the vaccine or related complications.

b. ***Phase II Studies***

The phase II studies can begin phase I have been completed satisfactorily. The phase II studies should define the optimum dose, the vaccination schedule, and most importantly, safety, prior to beginning phase III. The main objectives of these studies are to demonstrate the immunogenicity of the active component(s) and safety in the target population (mainly healthy children).

c. ***Phase III Studies***

The Phase III studies should provide data on the efficacy and safety of the vaccine in large populations. Serological data are collected (for at least one immunized population subgroup) with the idea of establishing a correlation between clinical efficacy and immunogenicity, although this cannot always be established.

The type of vaccine and other relevant factors (incidence of disease, immunological markers, and safety) will determine the duration of the follow-up on these studies and the number of participants.

The phase III clinical studies should be performed using at least three (3) lots manufactured on the industrial or production scale to be used routinely (in the majority of countries).

d. ***Phase IV Studies***

Depending on the type of application for marketing authorization, approval in other countries, or depending on the type of vaccine, a phase IV study protocol or the results of studies that have

already been performed, will be required. For new vaccines, a pharmacovigilance plan should be presented.

In submitting the data on clinical trials, due consideration must be made to following:

I. Populations requiring special considerations including renal and hepatic impairment

The clinical development programme should involve studies to support the approval in subpopulations such as patients with organ dysfunction. Whether such studies are necessary depends on the elimination characteristics of the compound. If no study is conducted, this should be justified by the applicant.

II. Other types of product requiring special considerations

Some types of data and testing are specific for certain types of product, such as genetic stability for recombinant vaccines, data concerning the inactivation and attenuation methods, demonstration of comparability of combination vaccines, contribution of adjuvants and safety/toxicity studies for particular vaccines. In case of monoclonal antibodies, test for identity, potency, Safety, Protein Content and other tests such as pH, Osmolality, Extractable volume, Sterility, Bacterial Endotoxins, Moisture content, should be assessed wherever appropriate as per the National regulatory guidelines/ pharmacopoeia.

The following are the studies that need to be submitted as a part of clinical assessment to the NRA:

a) Pharmacokinetic (PK) studies:

Pharmacokinetic studies might be applicable when new delivery systems are employed or when the vaccine contains novel adjuvants or excipients.

In general, the PKs (absorption, distribution and elimination) of rDNA-derived biotherapeutics should be characterized during single-dose and steady-state conditions in relevant populations.

b) Pharmacodynamic studies:

Pharmacodynamic studies should comprise of the immunogenicity studies that characterize the immune response to the vaccine. Therefore, focus on considerations for an appropriate range of immunogenicity studies that may be conducted throughout the clinical development programme. The applicant should justify the final range of tests performed, with an explanation of the rationale for each investigation, in the Clinical Overview.

III. Safety and Immunogenicity studies:

c) *General methodological considerations:*

Early clinical studies should provide sufficient information on the safety and immunogenicity of the antigenic components in a candidate vaccine in the target population, to identify the primary immunisation schedule and optimal dose to be evaluated in subsequent confirmatory studies of safety and immunogenicity and, where feasible and necessary, protective efficacy. An appropriate animal disease model may be used if available.

d) *Minimum requirements for immunological testing*:

Protocols should specify and give details of the methodologies used to evaluate immune responses to vaccination. These should be consistent across studies, validated (including the use of international standards such as those of WHO if available) and demonstrated to be reproducible. If changes to methodologies are unavoidable during the clinical development programme, adequate cross-validation data should be provided.

e) ***Immunogenicity in various types of possible recipients for the vaccine****:*

Potential effects on the vaccine immune response of various host factors (e.g. age, prematurity, maternal antibody, nutritional status, genetics, coexisting disease, immune suppression, and prior exposure to an infectious agent) should be considered.

f) Interaction studies:

Therapeutic proteins may influence the pharmacokinetics of conventional drugs metabolized by cytochrome P450 enzymes (CYPs) even if the proteins are not metabolized by CYPs. Therefore it is important that drug interaction studies are also conducted with therapeutic proteins, unless sufficient evidence is provided from published data or sufficient scientific rationale is provided on the basis of biological plausibility.

B. Clinical Evaluation of Similar Biologics (Biosimilars)

The clinical data should be generated using the product derived from the final manufacturing process and therefore reflecting the product for which marketing authorization is being sought. Any deviation from this recommendation needs to be justified and additional data may be required, such as from PK bridging studies comparing the PK profiles of the products from the previous and final formulations. For changes in the manufacturing process ICH quality guidelines '*Comparability of biotechnological/biological products subject to changes in their manufacturing process* (Q5E), 2004' should be followed.

Clinical studies should be designed to demonstrate comparable safety and efficacy of the biosimilar product to the reference product and therefore need to employ testing strategies that are sensitive enough to detect relevant differences between the products, if present.
The following are the documents/tests required for assessment:

1. **Evidence of registration with the respective National Regulatory Authority and or International NRA**

2. **Quality consideration**

a. Characterisation

Similar biologics should include physicochemical properties, biological activity, immunological properties, functional assays, purity (process-and product-related impurities etc.), contamination, strength, and content.

b. Specifications

Specifications of similar biologics must ensure consistency in product quality and comparability to reference biologic. Acceptance limits should be set based on reference biologic data and data from sufficient number of batches from preclinical or clinical batches.

c. Stability

To set a shelf-life and storage condition of drug product and drug substance, its real time stability test should be conducted. Stability studies on drug substance and drug product should be carried out using containers and conditions that are representative of the actual storage containers and conditions, according to relevant guidelines. Side-by-side accelerated and stressed studies comparing the similar biologic to the reference biologic will be of value in determining the similarity of the products by showing comparable degradation profiles.

d. Quality comparability study

The quality comparison between similar biologic and reference biologic is essential. The applicant should submit a full quality dossier including the results of comparability exercise for the similar biologic with the reference biologic before the applicant proposes to take the similar biologic to clinical development.

In case the isolation of the drug substance is not possible, comparability can be demonstrated at the drug product level with appropriate scientific justification. Differences between the similar biologic and the reference biologic should be evaluated for their potential impact on safety and efficacy of the similar biologic and additional characterization studies may be necessary. Appropriate data should be submitted to verify that these differences do not impact on the safety and efficacy.

3. Preclinical studies

These preclinical studies should be comparative in nature and designed to detect differences if any, between the similar biologic and reference biologic. The preclinical study design may vary depending upon the clinical parameters such as therapeutic index, the type and number of indications applied.

The dosage form, strength and route of administration of the similar biologic should be the same as that of the reference biologic and in case of any differences in these parameters, it should be justified.

a. Prerequisite before conducting preclinical studies

The applicant should produce the data generated along with the following basic clinical information and preclinical study protocols. The toxicology studies should be initiated after obtaining clinical study protocols.

i. Basic information about the reference biologic

- Information about the drug, route of administration, absorption and elimination rate, therapeutic index, dose, vehicle, mode of administration, dose response etc.
- Bioequivalence range, if available
- Tissue-specific localization, if available
- Available toxicity data on reference biologic
- Mode of action

ii. Basic information about the similar biologic

- Known/proposed clinical use

- Target population (Age, sex, pregnancy, lactating, children etc.)
- Dosage (frequency and intervals) –units
- Route/alternate routes of administration
- Final formulation + adjuvants, additives etc. - Toxicology data of adjuvants
- Diluents
- Presentation e.g. pre filled syringe

b. Studies required for preclinical evaluation:

i. Pharmacodynamic studies

- *In vitro* studies: Comparability of test and reference biologic should be established by *in vitro* cell based bioassay.
- *In vivo* studies: *In vivo* evaluation of biological/ pharmacodynamic activity may be dispensable if *in vitro* assays are available, which are known to reliably reflect the clinically relevant pharmacodynamic activity of the reference biologic. In cases where the *in vitro* assays do not reflect the pharmacodynamics, *in vivo* studies should be performed.

ii. Toxicological studies

In case of *in vivo* toxicity studies, at least one repeat dose toxicity study in a relevant species is required to be conducted. Regarding the animal models to be used, the applicant should provide the scientific justification for the choice of animal model(s) based on the data available in scientific literature. The dose should be calculated based on the therapeutic dose of the reference biologic. If required a pilot dose response study should be conducted prior to initiating the toxicity studies.

The protocols and the study reports should provide complete details of various steps in the toxicity testing as indicated below:

- Procedures prior to euthanasia e.g. blood drawing, body weight, etc.
- Events immediately after euthanasia, necropsy, gross – description, organ weights and organs sampled for histopathology.
- Biochemical parameters – Equipment and methods used - units of measurement and expression.
- Haematology procedures and parameters – method to be used (automated or manual).
- Statistical methods used.
- Bone marrow either examined as an aspirate /smear or on histopathology section.

iii. Immune responses

Antibody response to the similar biologic (vaccines) should be compared to that generated by the reference biologic in suitable animal model. The test serum samples should be tested for reaction to host cell proteins.

4. Clinical studies

Besides the information submitted in the preclinical application, the applicant has to submit application for conduct of clinical trial as per relevant NRA. The quality data submitted should establish comparability of similar biologic manufactured at clinical scale against reference biologic.

a. Pharmacokinetic (PK) Studies

Comparative pharmacokinetic studies should be performed in healthy volunteers or patients to demonstrate the similarities in pharmacokinetic characteristics between similar biologic and reference biologic on case to case basis.

The design of comparative pharmacokinetic studies should take the following factors into consideration.

- Half life
- Linearity of PK parameters
- Endogenous levels and diurnal variations of similar biologic under study(where applicable)
- Conditions and diseases to be treated
- Route(s) of administration, and
- Indications
- Appropriate design considerations can be combined into single dose or multiple dose studies with adequate justification. These design considerations include:
- Single dose, comparative, PK studies
- Parallel arm or
- Cross over
- Multiple dose, comparative parallel arm steady state PK studies

b. Pharmacodynamic (PD) Studies

As for the PK studies in the similar biologic clinical development program, the pharmacodynamic studies should also be comparative in nature. Comparative, parallel arm or cross-over, PD study in most relevant population (patients or healthy volunteers) is required for detecting differences between reference biologic and similar biologic.

c. Confirmatory Safety and Efficacy Study

Information to establish comparative safety and efficacy in relevant patient population is mandatory for all similar biologics.

Comparative clinical trials are critical to demonstrate the similarity in safety and efficacy profiles between the similar biologic and reference biologic with few exceptions (e.g. recombinant human soluble insulin products for which only comparative clinical safety study is required).

d. Safety and Immunogenicity Data

Both pre-approval and post-approval assessment of safety is desired to be conducted for similar biologic. Regarding pre-approval safety assessment, comparative pre-approval safety data including the immunogenicity data is required for all similar biologics including those for which confirmatory clinical trials have been waived. This pre-approval safety data is primarily intended to provide assurance of the absence of any unexpected safety concerns.

e. Extrapolation of Efficacy and Safety Data to other Indications

Extrapolation of the safety and efficacy data of a particular clinical indication (for which clinical studies has been done) of a similar biologic to other clinical indications may be possible if following conditions are met:

- Similarity with respect to quality has been proven to reference biologic

- Similarity with respect to preclinical assessment has been proven to reference biologic
- Clinical safety and efficacy is proven in one indication
- Mechanism of action is same for other clinical indications
- Involved receptor(s) are same for other clinical indications.
- New indication not mentioned by innovator will be covered by a separate application

C. Clinical Evaluation of Blood and Blood Products

Blood and blood components should comply with specifications and their testing should be performed using test methods approved by the NRA. All processes including data transfers and computerized systems that have an influence on the quality of the products in the area of collection, preparation or testing of blood and blood components should be validated. For critical processes such as rapid freezing of plasma, the need for revalidation should be defined. Quality control of blood and blood components should be carried out according to a defined sampling plan based on statistical methods.

Acceptance criteria should be based on a defined specification for each type of blood component. As an example for **fresh frozen plasma**, these data may include monitoring of **weight/volume, sterility, Factor VIII activity and residual cell counts (platelets, leukocytes, erythrocytes).** The work record should identify the test(s) employed so as to ensure that entries, such as the calculation of results, are available for review. Test results that do not meet the acceptance criteria should be clearly identified to ensure it is selected for further testing. An investigation should be conducted into the cause of failure prior to additional or repeat testing. Where possible, the performance of the test procedures should be regularly assessed by participation in a formal system of proficiency testing.

The following documents are required for clinical assessment:

1. **Evidence of registration with the respective NRA and or International NRA.**
2. **Clinical data listed below**

a. Platelet Survival in Circulation

i. Prolonged in vivo circulation survival of transfused platelets has been taken as a sign of a functional, undamaged platelet. Any new procedure for platelet collection and storage which does not demonstrate significant changes in platelet responses on in vitro tests should be further tested for its effects on platelet in vivo survival.

ii. In vivo animal tests may be necessary for definition of efficacy and safety of platelet substitutes. These should include an evaluation of the following aspects:

b. Evaluation of prothrombotic potential

A thrombosis model(s) in normal animals and in animals with disseminated intravascular coagulation (DIC) should be used for testing, since these conditions will be encountered clinically.

c. Evaluation of immunogenicity

Infusion of only sub cellular parts of the platelet may induce an immunogenic response. It should be demonstrated in test animals that the platelet substitute is no more immunogenic than intact platelets.

d. Additional toxicity due to platelet additives

Chemicals that are used to produce platelet substitutes and remain in the final product should be evaluated for toxicity, mutagenicity, and carcinogenicity at plasma concentrations expected to be reached in a recipient of multiple platelet substitute transfusions, as could occur with a platelet-refractory patient. It should also be recognized that platelet substitutes, like platelets, will be given to recipients in their reproductive years and that reproductive toxicology and teratology studies on the additives may also need to be done. It should also be noted whether the additives interfere, such as by adding color to plasma, with common clinical laboratory test determinations.

PRIORITY REVIEW FOR REGISTRATION

1. Subjected to fulfillment of the documents, the dossier for which the application for priority was received will be assessed first and preferably before other dossiers.
2. The request for priority review should be made at the time of submitting the dossiers along with justification which warrants priority review. DRA, however reserves the right to deny a request for priority review as deemed appropriate. This will be communicated to the applicant.

RESPONSIBILITY OF MARKETING AUTHORIZATION HOLDER, MAH

The applicant is responsible:

1. For the product and all information supplied in support of his application for registration of the product.
2. For updating any information relevant to the product/application. The DRA should be informed in a timely manner any change in product information during the course of evaluation, and after product registration, if the information pertains to rejection/withdrawal, additional data on product efficacy and safety or current Good Manufacturing Practice compliance of the manufacturers.
3. To notify the Authority on any changes related to products' quality, efficacy or safety throughout the product's life cycle in the country.
4. For the quality, safety and efficacy of his/her products.
5. For ensuring that the product imported for local sale and supply is identical, in all aspects, to that supplied at the time of registration. Any change in the product particulars must be notified to DRA and approval obtained before import.

FEES FOR REGISTRATION

1. **Processing fee:** Every application for registration should be accompanied with a processing fee of Nu. 150.00 (One Hundred and Fifty only).

2. **Registration fee:** The registration fee of Nu. 1500.00 (One Thousand Five Hundred only) per product should be paid at the time of issuance of registration certificate.

3. **Other charges:**
   a. The Authority may charge any applicant such costs as it may incur for the purpose of carrying out laboratory investigation if and when necessary prior to registration of the product
   b. Any payment made is not refundable once an application has been submitted and payment confirmed. Applications without the correct fees will not be processed.

The fees for registration of the products may be revised from time to time by the DRA. In such case, the public should be notified.

MULTIPLE APPLICATIONS

A separate application is required for each product i.e. products containing the same ingredients but made to different specifications (in terms of strength/content of ingredient(s), dosage form, description, pack size etc.) or by a different manufacturer.

PROCESSING OF APPLICATIONS

1. Initiation of Review

Review of applications will follow a queue system.

2. Stop Clock

a. The clock starts once payment has been confirmed for a submitted application and will stop whenever DRA needs to seek further information from the applicant. The clock restarts when the DRA receives complete responses from the applicant.
b. A period of 6 (six) months will be given within which the applicant should submit the additional information/clarification required for each correspondence from DRA.
c. The clock stops when the DRA informs the applicant of its regulatory decision.

3. Rejection of the application

a. An application for registration will be rejected in following cases:
   i. If the applicant fails to respond to the enquiries or submit the required additional documents within six (6) months from the last correspondence date. ***OR***
   ii. The applicant fails to submit all the required documents and complete the registration formalities within one (1) year.
b. Once the application is rejected, the applicant will be informed and the dossiers will be handed over to the applicant.
c. If the applicant wishes to re-process the same, the application must be re-submitted along with complete set of documents and token fee. The dossier will then be considered new.

REGULATORY DECISION

1. Decisions of the Drug Regulatory Authority

A regulatory decision is made based on the outcome of the evaluation of the dossier by the committee for registration of the product. The decision will be accordingly communicated to the applicant.

2. Product Registration Number

When a product application is deemed to have satisfied the registration requirements of quality, safety and efficacy; a registration number specific to the product will be given after getting approval from the Drug Controller.

3. Issuance of Registration Certificate

a. The certificate for registered product will be issued in the specified format.
b. The registration certificate should be issued within 30 working days from the date of receipt of complete required documents unless otherwise a longer period is required, in which case, the party will be informed.
c. The time-frame for registration for all categories of products excludes stop-clock time.

4. Validity of the Product Registration Certificate

The registration of a product should be valid for a period of three (3) years and should be specified on the certificate.

5. Rejection, Cancellation, Suspension of Registration

The Bhutan Medicines Board may reject, cancel or suspend the registration of any product if there are deficiencies in safety, quality or efficacy of the product or failure to comply with conditions of registration.

6. Appeal against Regulatory Decisions

Any applicant aggrieved by the Regulatory Decisions may submit a written petition to the Bhutan Medicines Board within thirty (30) days from the date of issue of the decision as per chapter XVII of the Bhutan Medicines Rules and Regulation 2012.

CANCELLATION OF REGISTRATION

The Authority may, in the interest of public safety, reject or cancel the registration of any product, if:

1. Any of the conditions of registration of the product has been contravened. This may include the mismatch between the documents submitted at the time of registration and physical GMP audit;
2. Any report on adverse drug reactions of serious nature have been received from National Pharmacovigilance Centre or any other national or international sources;
3. MAH defaults timely renewal beyond three month of grace period;
4. Manufacturer or MAH obstructs the inspection of the Manufacturing firms or premises; Or
5. For any other matters as specified by the Board at the time of cancellation.

Such products may not be imported, manufactured, sold, supplied or possessed for sale.

RENEWAL OF REGISTRATION

1. Application for renewal should be submitted in form VIII-PRR (attached as Annexure 3 to this guideline) of the regulation at least 30 days before expiry date of registration along with the application fee.
2. A grace period of three months may be given if the current MAH provides a written justification with evidence of having carried out the renewal process with the manufacturers prior to the date of expiry.

3. Upon the completion of the grace period or failure to provide the evidence, the product will be deemed deregistered from the actual registration expiry date. Once de-registered, the application will be considered new and full documents must be submitted.
4. The renewal with conditions and documents prescribed below is applicable only to the medicines which are evaluated via full registration route.
5. The medicines which were evaluated via abridged evaluation route will be renewed upon submission of complete set of documents as initial registration.
6. The procedure for the renewal of the registration is same as the initial registration. However, one time renewal of registration should be granted with the fulfillment of the following conditions and documents.

7. Condition for renewal

a. For renewal with minimal documents, it is mandatory that there should not be change in the:

i. manufacturing site/premise of the particular product;
ii. ingredients used for the formulation of the particular product;
iii. formulation including colour, size and dosage forms;
iv. indication and the information on the package insert;
v. type of packaging, packaging material or other packaging specifications

8. Documents required for renewal

a. If all the above conditions for the renewal are fulfilled; one time renewal will be done on submission of the Part I (General Documents) for full evaluation and Certificate of analysis for the finished product.

Note: The description on above document is provided under data requirements for full registration

PRODUCT REGISTRATION TRANSFER

1. The market authorization of the registered product may be transferred to another individual or firm authorized by the DRA. However, following conditions and data requirements for product registration transfer must be fulfilled.

2. Conditions:

a. An application to transfer the marketing authorization of a product must be submitted by the proposed new MAH.
b. The principal manufacturer agrees to withdraw the authorization granted previously to the existing MAH and issue new letter of authorization to the proposed new MAH.
c. The existing product registration shoulld have a remaining validity period of at least one (1) month. If the period is less than one month, the product must be renewed by the existing MAH before the transfer application is submitted.

3. Data Requirements:

a. The original letter of authorization from the principle manufacturer including the name of the product(s) to the proposed MAH.
b. No objection certificate/letter from the current MAH of the product.

4. If without any justifiable reason, the existing market authorization denies to give No Objection certificate/letter, the Authority may consider the letter of authorization as sole documentation requirement for change of MAH.
5. Once the Product Registration has been transferred, the new licensee will be responsible for all matters relating to the product registration and product performance.
6. No fee will be charged for the application and the outcome of the transfer application will be notified to both the existing and new Authorization Holder.

CHANGE IN THE PARTICULARS OF THE REGISTERED PRODUCT- POST REGISTRATION CHANGES

1. No change in product name, product specifications, packing, indications, contents of product label, package insert, or product literature, or any relevant particulars of the registered product should be made without the prior approval of the Authority.

2. The MAH may apply to the authority for any post registration changes during the valid period of registration using form no. VIIa-PRC attached as Annexure 4.

3. Only following post registration change is accepted. The change must be submitted with supporting document as indicated against each proposed change:

Type of post registration change: Change in product name	
Conditions to be fulfilled	There is no change to the product (formulation, release and shelf-life specifications, manufacturing source and process etc) except for the product name change.
Documents to be submitted	1. Official letter from principle manufacturer requesting for the change of product name 2. A declaration letter from the manufacturer and MAH that there is no other changes to the product/label except for the finished product name change. 3. Revised draft package insert and label incorporating the proposed variation. 4. Updated Certificate of Pharmaceutical Product (CoPP) (where applicable). 5. Product Sample with proposed name, the quantity as defined above under data requirements

Type of post registration change: Change in the specimen of Package Insert, Patient Information Leaflet, unit carton label, inner label and/or blister strips. Includes: Change of the layout/artwork Addition/deletion/replacement of pictures, diagrams, bar code, logos and/or texts on the package and label Change in information in the insert	
Conditions to be fulfilled	There is no change to the product (formulation, release and shelf-life specifications, manufacturing source and process etc) except for the above specified change.
Documents to be submitted	1. Official letter from principle manufacturer requesting for the change of product name 2. Proposed product labeling, a clean and annotated version highlighting the changes made. 3. Letter of declaration from the manufacturer and MAH stating that no other changes on the label except for the intended change. 4. Relevant document/reference to support the changes (where applicable).

	5. Product Sample with proposed change, the quantity as defined above under data requirements

Type of post registration change: Change of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile product	
Conditions to be fulfilled	1. Shelf-life specifications of the finished product remain unchanged. 2. The new size is consistent with the dosage regimen and duration of use as approved in the package insert. 3. The change only concerns the same packaging type and material.
Documents to be submitted	1. Justification for the proposed pack size. 2. Revised drafts of the package insert and labeling incorporating the proposed changes (where applicable). 3. Stability data at zone IV for atleast 3 different batches. Both real time and accelerated stability test report must be submitted. 4. Price structure for the new pack 5. Information and data on package and label 6. Letter of declaration from the manufacturer and MAH stating that no other changes on the label except for the intended change. 7. Certificate of analysis for the finished product 8. Product Sample with proposed change, the quantity as defined above under data requirements

Type of post registration change: Change of outer carton pack sizes for a finished product	
Conditions to be fulfilled	1. Primary packaging materials remain unchanged. 2. No other changes except for the change of outer carton pack sizes for a finished product.
Documents to be submitted	1. Revised drafts of the outer carton pack and labeling incorporating the proposed variation (where applicable). 2. Letter of declaration from the manufacturer and MAH stating that no other changes except for the change of outer carton pack sizes for a finished product. 3. Product Sample with proposed change, the quantity as defined above under data requirements

Type of post registration change: Change in any part of the (primary) packaging material not in contact with the finished product formulation such as colour of flipoff caps, colour code rings on ampoules	
Conditions to be fulfilled	The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.
Documents to be submitted	1. Information and data on package and label 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Letter of declaration from the manufacturer and MAH stating that no other changes except for the intended change.

	4. Price Structure, if changed 5. Product Sample with proposed change, the quantity as defined above under data requirements

Type of post registration change: Reduction of shelf-life of the finished product a) As a package for sale and/or b) After first opening and/or c) After dilution/reconstitution	
Conditions to be fulfilled	1. For (a) & (b) - The studies must show conformance to the currently approved shelf-life specification. 2. For (c) – The studies must show conformance to the currently approved shelf life specification for the reconstituted product.
Documents to be submitted	1. Results of appropriate real time stability studies covering the duration of proposed shelf-life of at least two pilot/production scale batches of the product in the authorized packaging material 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Justification letter for the change of shelf-life of the finished product (where applicable). 4. Letter of declaration from the manufacturer and MAH stating that no other changes on the label except for the intended change.

Type of post registration change: Change of the name or address (for example: postal code, street name) of the manufacturer of finished product	
Conditions to be fulfilled	1. The manufacturing site remains the same. 2. Not applicable to the case in which it involves change in ownership of the manufacturer. 3. No other changes except for the change of the name and/or address of a manufacturer of the finished product.
Documents to be submitted	1. Official letter from the manufacturer requesting for the change in name/address of the plant. 2. A valid GMP certificate, CoPP which covers the GMP certification or official document from relevant authority confirming the new name and/or address. 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 4. Letter of declaration from the manufacturer and MAH stating that no other changes on the label except for the intended change. 5. Product Sample with proposed change, the quantity as defined above under data requirements 6. Price Structure, if applicable

Type of post registration change: Change in storage conditions	
Conditions to be fulfilled	There is no change to the product except for the intended change

Documents to be submitted	1. Stability test report 2. Letter of declaration from the manufacturer and MAH stating that no other changes on the label except for the intended change. 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 4. Product Sample with proposed change, the quantity as defined above under data requirements

Type of post registration change: price structure	
Conditions to be fulfilled	There is no change to the product except for the intended change
Documents to be submitted	Price structure of the product

Type of post registration change: additional indication	
Conditions to be fulfilled	
Documents to be submitted	1. Letter of declaration from the manufacturer and MAH stating that no other changes on the label except for the intended change. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Product Sample with proposed change, the quantity as defined above under data requirements 4. Price structure, if applicable

Type of post registration change: Change of Product Labeling due to Safety Updates	
Conditions to be fulfilled	The change relates to tightening of the product's target-patient population - The change is an addition of warnings, precautions, contraindications or adverse events/effects to the approved product labels
Documents to be submitted	1. Official letter stating: (a) the reasons for the notification, *AND*, (b) the status of the proposed changes in other countries; 2. Letter of declaration from the manufacturer and MAH stating that no other changes on the label except for the intended change and that the changes are supported by data 3. Product Sample with proposed change, the quantity as defined above under data requirements

Type of post registration change: Change of Pharmacoepial Standard of the finished product	
Conditions to be fulfilled	There is no change to the product (formulation, release and shelf-life specifications, manufacturing source and process etc) except for the intended change.
Documents to be	1. Official letter from manufacturer authorizing the change of

submitted	pharmacoepial standard 2. A declaration letter from the manufacturer and MAH that there is no other changes to the product/label except for the change in the Pharmacoepial Standard. 3. Revised draft package, insert and labeling incorporating the proposed change. 4. Updated Certificate of Pharmaceutical Product (CoPP) (where applicable). 5. Price structure, if applicable 6. Product Sample with proposed change, the quantity as defined above under data requirements

Annexure 1: Application forms for Abridged Registration of the Biologics

Form No.: V-PAR
Regulation No.: 35 &38

APPLICATION FOR ABRIDGE REGISTRATION OF MEDICINES

I/we ……hereby apply for abridge registration of the product specified below for sale/distribution in Bhutan.

The product is been approved by the following referenced drug regulatory agency or agencies (*Circle the appropriate agency*);

i. Australia Therapeutic Goods Administration (TGA);
ii. Health Canada (HC);
iii. US Food and Drug Administration (FDA);
iv. European Medicines Agency (EMA)
v. UK Medicines and Healthcare Products Regulatory Agency (UK MHRA)
vi. Japan DRA
vii. Health Science Authority of Singapore (HSA)
viii. Drug Control Authority of Malaysia (BPFK)
ix. Thai FDA
x. WHO/OIE/other recognized agency(*please specify*)

Details of Medicinal Product (s)

Product	Pack	Composition (With Strength)	Manufacturer

Proposed name of the Market Authorization Holder:

Application fee has been deposited to the Royal Government of Bhutan vide Revenue Receipt no ……. (*Attach copy*)

Declaration (please tick the boxes):

☐ I hereby declare that the documents submitted above/all information provided is true to my knowledge and will be liable for any consequences if any information provided is proved to be false or misleading.

☐ If my application is granted, I should abide by the Medicines Act and Medicines Regulations and any other standards set by the Authority.

Signature of applicant: ……
Name:……
Date: ……..... Address:……

Annexure 2: Application forms for Full Registration of the Biologics

Form: **VI-PFR**
Regulation Section: **36 & 38**

APPLICATION FOR FULL REGISTRATION OF MEDICINES

I/we ……hereby apply for registration of the product specified below for sale/distribution in Bhutan.

Type of medicines (*Circle the appropriate one*): i. Allopathy ii. gSo-ba-Rig-ba

Details of Medicinal Product (*Use one application per product*)

Product	Pack	Composition (With Strength)	Manufacturer

Proposed name of the Market Authorization Holder:

Application fee has been deposited to the Royal Government of Bhutan vide Revenue Receipt no ……. (*Attach copy*)

Declaration (please tick the boxes):

☐ I hereby declare that the documents submitted above/all information provided is true to my knowledge and will be liable for any consequences if any information provided is proved to be false or misleading.

☐ If my application is granted, I should abide by the Medicines Act and Medicines Regulations and any other standards set by the Authority.

Signature of applicant: ……
Name: ……
Address: ……

Date: ……

Annexure 3: Application form for Renewal of Registration of the Biologics

Regulation Section: 46(a)

APPLICATION FOR RENEWAL OF REGISTRATION OF MEDICINES

I/we ……hereby apply for renewal of registration of the product specified below for sale/distribution in Bhutan.

Product Registration no.

Name of the product:

Pack Size:

Date of Expiry of the Registration:

Pack	Composition (With Strength)	Manufacturer

Name of the Market Authorization Holder:

Details of the documents attached:
……
……
Application fee has been deposited to the Royal Government of Bhutan vide Revenue Receipt no ……. (Attach copy)

Declaration (please tick the boxes):

☐ I hereby declare that the documents submitted above/all information provided is true to my knowledge and will be liable for any consequences if any information provided is proved to be false or misleading.

☐ If my application is granted, I should abide by the Medicines Act and Medicines Regulations and any other standards set by the Authority.

Signature of applicant: ……
Name: ……
Address :……

Date:……

Annexure 4: Application form for Post Registration Changes of the Biologics

Form: **VIIa-PRC**
Regulation Section: **44 (a)**

APPLICATION FOR POST REGISTRATION CHANGES OF MEDICINES

I/we ……hereby apply for post registration of the product for the details below:
Product registration number:

Name of the product:

Proposed Changes (*Circle the appropriate changes*):

a. Shelf life or stability data
b. Packaging specification
c. Pack sizes
d. Dosage regimen
e. Additional indication and target species
f. Price structure
g. Market authorization holder and/or
h. other minor changes(*Please specify the details*)

Name of the Market Authorization Holder:

Declaration (please tick the boxes):

☐ I hereby declare that the documents submitted above/all information provided is true to my knowledge and will be liable for any consequences if any information provided is proved to be false or misleading.

☐ If my application is granted, I should abide by the Medicines Act and Medicines Regulations and any other standards set by the Authority.

Signature of applicant: ……
Name: ……
Address: ……

Date: ……..

Annexure 5: List of relevant international guidelines

1. 'World Health Organization Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations'. WHO Technical Report Series No. 924, 2004.

2. Guidelines for assuring quality of DNA vaccines. In: WHO Expert Committee on Biological Standardization. Forty-seventh report. Geneva, World Health Organization, 1998, Annex 3 (WHO Technical Report Series, No. 878).

3. Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology. In: WHO Expert Committee on Biological Standardization. Forty-first report. Geneva, World Health Organization, 1991, Annex 3 (WHO Technical Report Series, No. 814).

4. Guidelines for the production and quality control of synthetic peptide vaccines. In: WHO Expert Committee on Biological Standardization. Forty-eighth report. Geneva, World Health Organization, 1999, Annex 1 (WHO Technical Report Series, No. 889).

5. Committee for Medicinal Products for Human Use. *Guideline on similar biological medicinal products*. London, European Medicine Evaluation Agency, 2005 (CHMP/437/04).

6. Woodcock J, Griffin J, Behrman R, Cherney B, Cresoenzi T, Fraser B, et al. FDA's assessment of follow-on protein products: a historical perspective. *Nature Reviews Drug Discovery*, 2007, 6:437-42.

7. Committee for Medicinal Products for Human Use. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues*. London, European Medicine Evaluation Agency, 2006 (CHMP/BMWP/49348).

8. Committee for Medicinal Products for Human Use. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance : non-clinical and clinical issues*. London, European Medicine Evaluation Agency, 2006 (CHMP/BMWP/42832).

9. ICH safety guidelines. *Preclinical safety evaluation of biotechnology-derived pharmaceuticals* (S6), 1997.

10. ICH quality guidelines. *Comparability of biotechnological/biological products subject to changes in their manufacturing process* (Q5E), 2004.

11. Committee for Medicinal Products for Human Use. *Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins*. London, European Medicine Evaluation Agency, 2007 (CHMP/BMWP/14327).

REFERENCES

1. *Guideline on quality, non-clinical and clinical assessment of vaccines in Thailand.* Thailand Food and Drug Administration, 2008.

2. Expert Committee on Biological Standardization. *Guidelines on evaluation of similar biotherapeutic products (SBPs).* Geneva, World Health Organization, 2009.

3. WHO technical report, series no. 924. *Guidelines on clinical evaluation of vaccines: regulatory expectations.* World Health Organization, 2004.

4. WHO technical report, series no. 850. *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products.* World Health Organization, 1995.

Checklist for preparation and submission of the dossier for Full Evaluation route

	Mark (√) if Attached
Part I-General Documents	
1) Company profile	
2) cGMP Certificate	
3) Manufacturing License	
4) CoPP	
5) Letter of Authorization from the manufacturer *(if the dealer is involved)*	
6) Evidence of Free Sale	
7) Price Structure	
8) Letter of Evidence	
9) Product Sample (Qty as specified by DRA)	
10) Specimen of Package including package, label and insert (3 Specimens)	
Part II- Product profile	
1) Product profile	
Part III-Quality profile ***A. Drug substance as raw materials***	
1) Composition of the product	
2) Description of the manufacturing facility	
3) Method of manufacture	
4) Detailed description of the source of raw materials	
5) Process controls	
6) Manufacturing consistency	
7) Immunogenic substance specifications	
8) Reprocessing	
9) Container and closure system	
10) Immunogenic substance stability	
B. Manufacturing process, quality, safety, efficacy & non-clinical aspects	
1) Manufacturing process	
2) Quality	
3) Safety	
4) Efficacy	
Part IV--Pharmacological Documents ***1. For Vaccines***	
1) Vaccine type	
2) Evidence of registration with the respective National Regulatory Authority and or International NRA	

3) Phase I study reports	
4) Phase II study reports	
5) Phase III study reports	
6) Phase IV study reports	
7) Requirements for special population groups	
8) Side effects	
2. For Biosimilars	
1) Evidence of registration with the respective National Regulatory Authority and or International NRA	
2) Quality consideration	
3) Quality comparability study	
4) Preclinical studies requisites	
5) Preclinical studies reports	
6) Clinical studies reports	
3. For Blood and blood products	
1) Evidence of registration with the respective NRA and or International NRA	
2) Clinical data	