

GUIDELINE FOR REGISTRATION OF BIOLOGICS FOR VETERINARY USE

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REVISION HISTORY

This guideline supersedes the Data Requirement for Biologics and Biotechnology Products in the 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
CoPP:	Certificate of Pharmaceutical Product
NRA:	National Regulatory Authority
MAH:	Market Authorization Holder
DRA:	Drug Regulatory Authority
DTAC:	Drug Technical Advisory Committee
CoA:	Certificate of Analysis
WHO:	World Health Organization
INN:	International Non-proprietary Name
rDNA:	recombinant DNA
ELISA:	Enzyme Linked Immuno Sorbent Assay
OIE:	Office International des Epizooties
FAO:	Food and Agriculture Organization

DEFINITION OF THE TERMINOLOGIES USED IN THIS GUIDELINE

- a. **Abride 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.
- b. **Adverse Event Following Vaccination** refers to any undesired or unintended response following vaccination.
- c. **Authority** refers to Drug Regulatory Authority of Bhutan.
- d. **Biologics** refers to a product whose active substance is made by or derived from a living organism (plant, animal or microorganism) and may be produced by biotechnology methods and other cutting-edge technologies. This product imitates natural biological substances intended for use in treatment and prevention of infectious diseases of animals or for purpose of research in animals.
- e. **Cell line** refers to a cell culture developed from a single cell and therefore consisting of cells with a uniform genetic make-up.
- f. **Compendia** refers to a collection of concise but detailed information about a particular subject, especially in a book or other publication.
- g. **Cytometric analysis** refers to the characterization and measurement of cells and cellular constituents.
- h. **Drug Technical Advisory Committee (DTAC)** refers to the committee appointed under section 5.1 of the Medicines Act of the Kingdom of Bhutan 2003.
- i. **Evaluation** refers to the assessment of the dossier and product sample submitted by the applicant using predefined set of criteria and checklist.
- j. **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.
- k. **General Document Evaluation** refers to the evaluation of part I under data requirement of full evaluation route in the dossier.
- l. **Good Manufacturing Practices (GMP)** refers to a system for ensuring that products are consistently produced and controlled according to quality standards (OIE).
- m. **Immunoblot** refers to a technique for or the blot resulting from, analyzing or identifying proteins via antigen-antibody specific reactions, as in Western blot technique.
- n. **Immunogen** refers to 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.
- o. **Market Authorization Holder** refers to a firm in whose name the product is registered/ licensed.
- p. **Neurovirulence testing** refers to the tendency or capacity of a microorganism to cause disease of the nervous system.
- q. **Neutralization assay** refers to the assay where neutralizing antibodies inhibit biological activity of a target, and cell viability or plaque reduction is the endpoint.
- r. **Primary cells** refer to a cell taken directly from a living organism, which is not immortalized.

- s. **Product Dossier** refers to the detailed biologics profile or technical documents generated from the biologics manufacturer for the purpose of biologics registration.
- t. **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.
- u. **Referenced NRA** refers to Drug Regulatory Authority which is referenced by DRA.
- v. **Registration Committee for product registration** refers to the committee as approved by the Board for evaluation of biologics(s).
- w. **Serotyping** refers to a group of organisms, microorganisms, or cells distinguished by their shared specific antigens as determined by serologic testing.
- x. **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.

SCOPE OF THIS GUIDELINE

In pursuant to Chapter VI section 16.2 of the Act, this guideline should apply to registration of following categories of biologics for veterinary use in Bhutan:

- a. Vaccines;
- b. Blood products;
- c. Monoclonal antibodies (therapeutics);
- d. Recombinant proteins including, but not limited to Insulins, Hormones, Erythropoietins and other hematopoietic factors, Cytokines: interferons, interleukins, colony-stimulating factors, tumour necrosis factors.

Although generally outlined for all the biologics in the scope of this guideline, the information on Product Profile (Part II) and Quality Profile (Part III) of disease specific vaccines should be provided as required in the Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2014 by the Organisation International des Epizooties (OIE) where a monograph for that product exists (under part C of each disease chapter).

Out of Scope:

This guideline doesn't apply to the following products:

- a. Diagnostic agents and test kits;
- b. Non-medicated bandages, surgical dressings, plaster, dental fillings;
- c. Instruments, apparatus, syringes, needles, sutures, catheters;
- d. Animal feed.

PROCEDURE FOR REGISTRATION APPLICATION

The route of biologics registration is broadly classified into abridged evaluation and full evaluation. In general, the biologics registration will follow full evaluation route while the abridged evaluation is granted for those biologics wherein the safety, efficacy and quality parameters of the specific biologics are evaluated by referenced NRA including the vaccines supplied by WHO, UN, OIE, FAO and other UN organizations. .

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

GENERAL REQUIREMENTS OF THE DOSSIERS

The dossier should be:

- a. Submitted typewritten or computer printed
- b. In English or Dzongkha or both
- c. Where originals are in another language, copies should be presented together with certified English translations.
- d. Be complete as per the specifications detailed in this guideline
- e. Containing a table of contents, the flow of information must be as per the flow of the document requirement in this guideline.
- f. Indexed to the various appendices
- g. Numbered on every page
- h. Properly bonded
- i. In A4 size paper
- j. Contain price structure of the biologics
- k. 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 document requirement for the registration will be based on the route of evaluation.

ABRIDGED REGISTRATION

Abridged evaluation should be applicable to;

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

DATA REQUIREMENTS FOR ABRIDGED REGISTRATION

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

A. Documentary evidence to support abridged evaluation:

1. Official approval letters or equivalent documents (like registration certificate for the said biologic) from the referenced NRA that certifies the registration status of the finished biologic. The certificate of registration issued by referenced NRA must be valid at the time of filing application; OR
2. Proof of pre-qualification or approval if the biologic is pre-qualified.

The above evidence must be provided either in original or notarized, if original copy is not available.

B. Declaration Letter

Official letter declaring that all aspects of the biologic's quality, safety and efficacy intended for sale 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

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 biologics authorized by the manufacturer to the dealer.
3. If the letter has provision of validity, the letter must be valid.
4. If the principal 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, Rupee or Ngultrum per unit pack size.

E. Product Sample

1. Samples of finished products 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 sample size may vary depending on the type of packaging used
4. 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 the original package including package, label and insert must be furnished same as commercially available specimens.
2. At least 3 specimens must be included in the dossier.
3. The product label should contain the following information:
 - 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. Pharmacopeial 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 different for different strengths of same product. 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

1. Full evaluation route is applicable to all categories of biologics which does not fulfill abridged evaluation criteria.
2. 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. However, if the biologics is manufactured in Bhutan; certifications like manufacturing license, CoPP, Evidence of Free Sale, cGMP etc issued by the Authority may not be necessary.

A. Company profile

The company profile of the principal *manufacturer for the finished product and raw materials* 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 (Heads of Production, Quality Control and Store) where possible with the signatures of the personnel against name.
5. List of the biologics manufactured.
6. State whether the company is manufacturing under loan license or not. If so, include details.

B. Current Good Manufacturing Practices (cGMP) certificate

cGMP certificate should:

1. Bear the Certificate number.
2. Bear the name of the firm, 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 OIE, FAO or WHO standards.

C. Manufacturing License

Manufacturing license should:

1. Bear the license number.
2. Bear the name of the firm, 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 OIE or 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 principal manufacturing firm may provide the authorization letter. In such case, the letter of authorization from the principle manufacturer to these offices should be submitted as well.

F. Evidence of Free Sale

If the CoPP format is not as per the format of OIE or 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:

1. Brand name
2. Generic name or International Non-proprietary Name
3. Dosage form and strength
4. Complete name and address of manufacturer

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, Rupee or Ngultrum 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 sample size may vary depending on the type of packaging used
4. 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 the original package including package, label and insert must be furnished same as commercially available specimens.
2. At least 3 specimens must be included in the dossier.
3. The product label should contain the following information:
 - 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. Pharmacopeial 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 different for different strengths of same products. The label must be made from good quality material.

PART II - PRODUCT PROFILE

1. Complete and concise summary of product particulars should be provided. 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. Strength of the finished product
 - v. Therapeutic category
 - vi. Mode of action
 - vii. Toxicology
 - viii. Indication
 - ix. Contraindications
 - x. Reconstitution
 - xi. Dose and dosage regimen
 - xii. Adverse Event Following Vaccination
 - xiii. Immunogenic interactions
 - xiv. Precaution(s)/warning(s)
 - xv. Storage condition(s)
 - xvi. Reference of the official standards of the finished product (e.g compendial pharmacopoeias or manufacturer's in-house specification).
 - xvii. 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
 - xviii. Description of the organoleptic characteristics of the product.
 - xix. 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 liquid, state clearly whether it is in the form of a solution (clear), suspension, emulsion, etc.
 - xx. Commercial presentation of packaging and pack size in terms of quantity/weight/volume, etc.

PART III - QUALITY PROFILE

A. Manufacture of active raw material used in production of biological product

1. General Considerations

- i. Manufacturers must prepare and submit two copies of details on production process. It must cite internationally accepted regulatory requirements such as that of the OIE or WHO. Once approved and stamped as satisfactory, one copy will be retained with the Authority, and one copy will be returned to the manufacturer.

- ii. The manufacturer presenting the product must provide a flow chart indicating the source(s) of all raw materials, antigens and /or other components.
- iii. The manufacturer is responsible for ensuring that all relevant and up-to-date standard operating procedures are submitted to the Authority.

2. Technical documents on raw materials

The master seeds used for the preparation of biologics must be demonstrated to be pure, safe and immunogenic by accepted test methods. Cell lines or primary cells if used, must provide evidence of being pure and safe. Serum, media or any other ingredients used in the preparation of the biologics must be demonstrated to be free of contaminants by accepted test protocols. The following requirements should be produced:

- i. A list of all active raw materials and manufacturer of these active raw materials
- ii. The method of manufacture of the active raw material in a flow chart along with;
 - a. Description of source, specifications and test methods of all antigens and/or components
 - b. Growth and harvesting
 - c. Purification and downstream processing
 - d. Manufacture of synthetic raw material
 - e. In process control specifications and tests at each stage of manufacture of active raw materials
- iii. Data on the molecular and biological properties of the raw material and details of their analytical methods.
 - a. For immunogenic raw materials, the description should include the biological name or chemical name, the source of the cells from which the raw material is derived, the active components of the cell fractions or purified antigens where applicable, and any chemical modification or conjugation of the immunogenic material.
 - b. For all raw materials, physical state, colour and clarity of the product must be described
 - c. Description of physico-chemical tests (identity, purity, assay for related proteins and process contaminants) and biological activity tests (specific identity testing such as immunoblots e.g. Western Blot or ELISA, cytometric analysis, neurovirulence testing, serotyping, electrophoretic typing, inactivation studies, neutralization assays, titrations, immunogenicity and potency) carried out on active raw materials must be furnished.

3. Certificate of Analysis (CoA) of raw materials

Validated and certified copies of the Certificate of Analysis from the supplier of raw materials or the manufacturer of the finished product should be included in the dossier.

- i. Be on a letterhead or other paper that adequately identifies the company manufacturing the raw material(s).
- ii. Name of the raw material.
- iii. Batch number of the raw material used in the manufacture of the finished product.
- iv. Be dated with the date of analyses and signed by an authorized person over his/her name.
- v. State the pharmacopoeial specifications and methods by which the tests are performed.
- vi. All tests and analyses that involve measurement should be reported as the actual numerical results and not as descriptions such as “compliant” or “pass”.
- vii. Results of tests for bioactive substance should include specific tests for identity, potency, purity, endotoxin and sterility.

B. Manufacturing process for finished products

1. General Considerations

- i. Comprehensive details of the procedures involved in the various stages of manufacture of finished product should be given. It should also include the frequency and sequence of analytical, microbiological and other in-process control procedures carried out during the manufacturing process.
- ii. The manufacturing process should be submitted in form of a detailed flow diagram accompanied by a list of equipment used at each stage. Stages of manufacture may include aseptic processing, sterilisation, lyophilisation, freeze-drying and packaging.

2. Analytical method for finished product

Analytical method for finished product should include the following:

- i. Technical/quality specification of the finished product.
- ii. A description of all test methods selected to assure the identity, purity, sterility, strength and/or potency, as well as the lot-to-lot consistency of

the finished product and the specifications. This should also include a description of tests/assays used for identification of preservatives and antioxidants.

- iii. Validation information, including experimental data for accuracy, specificity, precision, linearity and reproducibility of the analytical procedures.

3. Certificates of Analysis (CoA) of the finished product

- i. The CoA of the Finished Product should include the results of all the requirements and test methods stated in the technical/quality specification of the product. Certificates of analysis and analytical results for at least five consecutive batches should be provided.
- ii. The certificate, validated and certified should:
 - a. Be on a letterhead or other copy that adequately identifies the manufacturer of the product.
 - b. Be dated with the date of analyses and signed by an authorized person against the name.
 - c. State the specifications and methods against which and by which the tests are performed.
 - d. Give all tests and analyses that involve measurement as the actual numerical results and not descriptions like "complies" or "pass".
 - e. Declare acceptable in case of such document being computer generated.

4. Specifications of the packaging materials

The following information on the packaging materials should be provided:

- i. A general description of the container and the closure system including primary (inner) and secondary (outer) packaging and other components such as pack size, fill details and container type.
- ii. The chemical identity of the materials for each component of the packaging system and detail specifications and tests for materials of each primary packaging component.
- iii. Evidence of compatibility of the materials of construction with the finished product, including sorption to container and leaching, and/or safety of materials of construction.
- iv. A certificate of analysis as proof that the packaging conforms to specifications.

5. Stability studies on finished products

Evidence of stability of the product submitted should include the following information:

- i. Reports for both Accelerated Stability Study (Temperature $40\pm 20\text{C}$ and Relative humidity $70\pm 5\%$) and Real Time Stability Study (Temperature $30\pm 20\text{C}$ and Relative humidity $60\pm 5\%$).
- ii. The types of studies conducted, details of the protocols used, and the summary of the results of the studies. The summary should include results as well as conclusions with respect to proposed storage conditions and shelf life, in-use storage conditions and shelf life, retest date, as appropriate.
- iii. Results of the stability studies presented in an appropriate format such as tabular, graphical or narrative.
- iv. The interpretation of results and shelf life determinations should be based on the least stable batch.
- v. Labeling recommendations is reflected on the product samples submitted with the application.
- vi. 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.
- vii. 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.
- viii. 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.
- ix. Information on the stability program should include the following details:
 - a. Number of batches (minimum of 3 different batches) with the batch number.
 - b. Product composition
 - c. Container/closure system
 - d. Storage conditions

e. Testing intervals

f. Initial values

PART IV - PHARMACOLOGICAL DOCUMENTS

Objectives, experimental protocol, summarized results and conclusions of the studies performed to demonstrate all aspects of pharmacology of the product should be furnished.

A. Product Information Summary

1. The Product Information Summary should be consistent with information provided under Product Information Leaflet. It should include indications, target animal, age group, dosage and directions for use.
2. List of all the major and common side effects.
3. Information on the adverse effects of the product, the animals in which it shouldn't be used, precautions before or during use in certain animals should be provided.

B. Pharmacokinetics studies

1. Absorption, distribution, metabolism, excretion characteristics.
2. Relationships between pharmacokinetic characteristics and therapeutic and toxic effects.
3. Pharmacokinetic drug interactions observed or predicted.

C. Pharmacodynamic studies

1. Primary and secondary pharmacodynamics.
2. Safety pharmacology.
3. Pharmacodynamic drug interactions.

D. Developmental studies/field trials/other studies

Summary reports of developmental studies/field trials and other studies consisting of information on objectives, experimental protocol, summarized results and conclusions of the studies performed to demonstrate safety, efficacy and potency of the product should be furnished.

1. Non-reversion to virulence studies examining the effect of multiple back-passages in the target animal species demonstrating safety.

2. Results of inactivation test for inactivated products.
3. Data from immunogenicity and/or vaccination-challenge studies demonstrating efficacy.
4. Results of studies validating the proposed test procedures for potency testing.
5. Findings of the field trials of the final product, especially for safety and efficacy.
6. Findings of other studies conducted such as residue study, occupational health and safety study and environmental risk study (where applicable).

SHIPMENT, STORAGE AND DELIVERY

Maintenance of biological activity is generally dependent on 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. Product characteristics include potency, purity, physico-chemical, biochemical and immunological properties, visual appearance, evidence of additive or excipient degradation, and container/closure interactions.

The manufacturer or MAH should ensure the following requirements are fulfilled for the purpose of lot release of the imported biologics by the Authority.

- i. As a DRA prequalification scheme, manufacturers are expected to ensure that their packaging complies with the criteria specified for the specified product.
- ii. Any changes introduced in the packaging or the shipment procedures must be documented and evidence of validation produced.
- iii. Temperature monitoring electronic devices should be included in all shipments to monitor temperature during the entire shipment process.
- iv. Temperatures within the insulated container should be monitored using sensors and should remain within the tolerance of +/- 1°C.
- v. Product summary protocols.
- vi. Data should be supplied for all different container closure combinations that will be marketed.

EMERGENCY USE

Under certain circumstances such as in case of an outbreak of a disease for which there is no effective licensed veterinary biologics available, the Authority may consider an application for the import of an unlicensed biotechnology-derived veterinary biologics for emergency use. In these situations, the Authority will require information on the origin and nature of the product, together with data demonstrating its purity, potency and safety, in order to fully evaluate the imported biologics. In addition, the Authority may request data supporting the efficacy of the veterinary biologics in order to be confident in its risk-benefit analysis.

PRIORITY REVIEW FOR REGISTRATION

1. The priority review will be given in terms of the time viz., if such applications are received, the dossier evaluation will be given priority. However, the data requirements should be fulfilled.
2. The request for priority review should be made at the time of submitting the dossiers along with justification which warrants a priority review. The Authority, however reserves the right to deny a request for priority review if it is deemed appropriate. This will be communicated to the applicant.

RESPONSIBILITY OF MARKETING AUTHORIZATION HOLDER

1. The Market Authorization Holder (MAH) should be responsible for the product and all information supplied in support of his application for registration of the product.
2. MAH should be responsible for updating any information relevant to the product/application. The Authority 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 (cGMP) compliance of the manufacturers.
3. MAH should notify the Authority on any changes related to product's quality, efficacy or safety throughout the product's life cycle in the country.
4. MAH must assume responsibility for the quality, safety and efficacy of his/her products.
5. MAH is responsible 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 Authority and approval obtained before import.

FEES FOR REGISTRATION

The fees for registration of the products may be revised from time to time by the Authority and the public notified accordingly.

1. **Processing fee:** Every application for registration should be accompanied with a processing fee of Nu. 150.00 (Ngultrum One Hundred and Fifty only).
2. **Registration fee:** The registration fee of Nu. 1500.00 (Ngultrum One Thousand Five Hundred only) per product should be paid at the time of issuance of registration certificate.
3. **Other charges:**
 - i. 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.
 - ii. Any payment made is not refundable once an application has been submitted and payment confirmed. Applications without the correct fees will not be processed.

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 should require separate applications for product registration.

PROCESSING OF APPLICATIONS

1. Initiation of Review

Review of applications will follow a queue system.

2. Stop Clock

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

3. Rejection of the application

- i. An application for registration will be rejected if:

- a. The applicant fails to respond to the enquiries or submit the required additional documents within six (6) months from the last correspondence date. OR
 - b. The applicant fails to submit all the required documents and complete the registration formalities within one (1) year.
- ii. Once the application is rejected, the applicant will be informed and the dossiers will be handed over to the applicant.
 - iii. 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 Registration 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

- i. The certificate for registered product will be issued in the specified format.
- ii. The registration certificate will 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.
- iii. 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 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 Board within thirty (30) days from the date of issue of the decision as per chapter XVII of the Bhutan Medicines Rules and Regulation.

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 reactions of serious nature have been received from **pharmacovigilance centre** for veterinary medicines 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 PRODUCT REGISTRATION

1. Application for renewal should be submitted in form VIII-PRR of the regulation at least 30 days before expiry date of registration along with the processing 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 should 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 should 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.

A. Condition for renewal

The following mandatory conditions must be fulfilled by the product in question for renewal with minimal documents

1. There should not be change in the manufacturing site/premise of the particular product;
2. There should not be change in the ingredients used for the formulation of the particular product;
3. There should not be change in the formulation including colour, size, dosage forms and dosage;
4. There should not be change in indication and the information on the package insert;
5. There should not be change in the type of packaging, packaging material or other packaging specifications

B. Documents required for renewal

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 Authority. However, following conditions and data requirements for product registration transfer must be fulfilled:
 - i. An application to transfer the marketing authorization of a product should be submitted by the proposed new MAH.
 - ii. The manufacturer agrees to withdraw the authorization granted previously to the existing MAH and issue new letter of authorization to the proposed new MAH.
 - iii. The existing product registration should 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.
 - iv. The original letter of authorization from the principal manufacturer including the name of the product(s) to the proposed MAH.
 - v. No objection certificate/letter from the current MAH of the product.
2. 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.

3. Once the Product Registration has been transferred, the new licensee will be responsible for all matters relating to the product registration and product performance.
4. 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 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 for any post registration changes during the valid period of registration under the following procedure and conditions:
 - i. Apply to the Authority in form VIIa-PRC with proposed changes.
 - ii. Import the product only upon the confirmed incorporation of the post registration changes by the Authority.
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	<ol style="list-style-type: none"> 1. Official letter from principal 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

<p>Type of post registration change: Change in the specimen of Package Insert, Patient Information Leaflet, unit carton label, inner label and/or blister strips.</p> <p>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</p>	
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	<ol style="list-style-type: none"> 1. Official letter from principal 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

<p>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</p>	
Conditions to be fulfilled	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. Justification for the proposed pack size. 2. Revised draft of the package insert and labeling incorporating the proposed changes (where applicable). 3. Stability data at zone IV for at least 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. Revised draft 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 flip off 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	<ol style="list-style-type: none"> 1. Information and data on package and label 2. Revised draft 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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 draft 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.
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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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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 draft 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	<ol style="list-style-type: none"> 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 draft 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	
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Documents to be submitted	<ol style="list-style-type: none"> 1. Letter of declaration from the manufacturer and MAH stating that no other changes on the label except for the intended change. 2. Revised draft 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
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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	<ol style="list-style-type: none"> 1. Official letter stating: (a) the reasons for the notification, <i>AND</i>, (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 Pharmacopial 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 submitted	<ol style="list-style-type: none"> 1. Official letter from manufacturer authorizing the change of pharmacopial 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 Pharmacopial 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: CHECKLIST FOR PREPARATION AND SUBMISSION OF THE DOSSIER

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

<i>Part I-General Documents</i>	
Documents	Tick if submitted
Company profile	
cGMP Certificate	
Manufacturing License	
CoPP	
Letter of Authorization from the manufacturer (<i>if the dealer is involved</i>)	
Evidence of Free Sale	
Price Structure	
Letter of Evidence	
Product Sample (Qty as specified by Authority)	
Specimen of Package including package, label and insert (3 Specimens)	
<i>Part II - Product profile</i>	
Product profile	
<i>Part III – Quality profile</i>	
Technical documents for raw materials including specification, analytical method etc	
CoA of raw materials	
Manufacturing process inclusive of Batch Manufacturing Formula	
Analytical method for finished product	
CoA of finished product	
Stability test report (3 batches)	
a. Real time data (30±2 ⁰ C and RH of 60±5%).	
b. Accelerated data (40±2 ⁰ C and RH of 70±5%)	
Specification of package and label	
<i>Part IV – Pharmacological profile</i>	
Product Information Summary	
Pharmacokinetic studies	
Pharmacodynamic studies	
Summary reports of developmental studies/field trials and other studies	

**ANNEXURE 2: CHECKLIST FOR SUBMISSION AND
PREPARATION OF DOSSIERS THAT ARE REQUESTED FOR
EVALUATION VIA ABRIDGED EVALUATION**

Documents	Tick if you have included in the dossier
Documentary evidence to support abridged evaluation:	
Declaration Letter	
Letter of Authorization from the manufacturer	
Price Structure	
Product Sample	
Specimen of package, label and insert (3 specimens)	
Therapeutic indications-Product Information Summary	

NOTE:

1. Blank space reflects that the document is required

ANNEXURE 3: APPLICATION FORMS FOR REGISTRATION OF BIOLOGICS

Form No.: V-PAR

Regulation No.: 35 & 38

APPLICATION FOR ABRIDGE REGISTRATION OF MEDICINES

I/wehereby 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 shall abide by the Medicines Act and Medicines Regulations and any other standards set by the Authority.

Signature of applicant:

Name:

Address:

Date:

Form: VI-PFR
Regulation Section: 36 & 38

APPLICATION FOR FULL REGISTRATION OF MEDICINES

I/wehereby 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 shall abide by the Medicines Act and Medicines Regulations and any other standards set by the Authority.

Signature of applicant:
 Name:
 Address:

Date:

Form: VIIa-PRC**Regulation Section: 44 (a)****APPLICATION FOR POST REGISTRATION CHANGES OF MEDICINES**

I/wehereby 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 and pack sizes,
- c. Dosage regimen,
- d. Additional indication and target species,
- e. Price structure,
- f. Market authorization holder and/or
- g. 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 shall abide by the Medicines Act and Medicines Regulations and any other standards set by the Authority.

Signature of applicant:

Name:

Address:

Date:

Form: VIII-PRR**Regulation Section: 46(a)****APPLICATION FOR RENEWAL OF REGISTRATION OF MEDICINES**

I/wehereby 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 shall abide by the Medicines Act and Medicines Regulations and any other standards set by the Authority.

Signature of applicant:

Name:

Date:..... Address :.....

REFERENCES

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