GUIDELINE

Registration of Medicinal Products

DRUG REGULATORY AUTHORITY
ROYAL GOVERNMENT OF
BHUTAN
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REVISION HISTORY

This guideline supersedes the Guideline for Registration of the Medicinal Product, 2006. This guideline will be revised from time to time as deemed necessary by the Authority and Registration Committee members.

ABBREVIATIONS AND ACRONYMS

- cGMP: current Good Manufacturing Practice Certificate
- CoPP: Certificate of Pharmaceutical Product
- MAH: Market Authorization Holder
- DRA: Drug Regulatory Authority
- DTAC: Drug Technical Advisory Committee
- MRL: Maximum Allowable Residual Limit
- CoA: Certificate of Analysis
- WHO: World Health Organization
- INN: International Non-proprietary name
- USP: United States Pharmacopoeia
- BP: British Pharmacopoeia
- EP: European Pharmacopoeia
- JP: Japanese Pharmacopoeia
- BE: Bioequivalence
- BA: Bioavailability
- API: Active Pharmaceutical Ingredient
- GCP: Good Clinical Practices
- BCS: Biopharmaceutics Classification System
- AUC: Area Under Curve
- Vd: apparent volume of distribution
- t_{1/2}: Plasma half-life
- Cl: Clearance from the plasma
- LD_{50}: Lethal dose 50
ED$_{50}$: Effective dose 50
NOEL: No observable adverse effect level
ACT: Medicines Act of Kingdom of Bhutan 2003
Regulation: Bhutan Medicines Rules and Regulation 2012
Authority: Drug Regulatory Authority
Registration Committee: Registration Committee for Registration of the Medicinal Products

**DEFINITION OF THE TERMINOLOGIES USED IN THIS GUIDELINE:**

a. **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.

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

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

d. **Extemporaneous formulation** refers to pharmaceutical preparations compounded specifically for a patient.

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

g. **Good Manufacturing Practices (GMP)** refers to a system for ensuring that products are consistently produced and controlled according to quality standards (WHO).

h. **gSo-ba rig-pa medicines** refers to traditional medicines recognized by the Bhutan Medical and Health Council which are manufactured using the ingredients and methods as per the gSo-ba-rig-pa text for intended pSo-ba-rig-pa indication.

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

j. **Medicinal Products** means:
   a. All substances intended for internal or external use of human beings or animals and intended to be used in the diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals including vaccines and biologicals; and
   b. Active Pharmaceutical Ingredients.

k. **National Drug Committee/Veterinary Drug Committee** refers to a committee approved by the Ministry of Health or Ministry of Agriculture and Forest respectively for the purpose of reviewing national drug policy and selection of essential medicines to be used in the government institutional establishments.
l. **Orphan drug** refers to any medicinal product that is intended for the treatment of a rare disease or a disorder or medical condition in human beings or animals. It shall include the medicines required for treatment of neglected diseases.

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

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

o. **A newly introduced drug refers** to any medicinal products which are required in the country (as recommended by DTAC and approved by Board) but it still has not completed phase III clinical trials.

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

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

r. **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.
HOW TO USE THIS GUIDELINE

The guideline is formulated to help the potential Market Authorization Holder viz., manufacturer and Bhutanese firm certified by DRA in preparation of the dossier for registration of the medicinal product. This guideline also contains the application process and related information on registration process. Responsibilities of MAH are also detailed.

The document requirement for registration is broadly classified into 2 categories based on the type of evaluation viz., abridged evaluation and full evaluation. The document required for full evaluation is further classified into 9 categories based on the types of medicine as classified under ‘Guidance for classification of medicines’ section in this guideline. All the documents required for registration is detailed to guide the personnel involved in making dossiers and to minimize the communication gap.

For registration of medicines under abridged evaluation route, all the documents as required under ‘Data Requirements for Abridged Registration’ section of this guideline must be submitted.
In general, the documents under full evaluation are classified into 4 parts namely Part I-General Documents, Part II- Product Profile, Part III-Quality Profile and Part IV-Pharmacology profile). Part I and Part II are applicable to all the 9 categories of medicines, unless specified otherwise. Thus, is kept general.

Ex. For Registration of Amoxicillin 250mg Capsule (10 x 10 pack size) of ‘X’ manufacturer which doesn’t qualify for registration under abridged evaluation; all the documents specified under Part I, II, III and IV must be fulfilled. Part I and II are specified as general (applicable to all 9 categories of medicines) while Part III and IV are specified under ‘Data Requirements for Human Allopathic Medicine’ of this guideline.
Similarly for registration of veterinary medicine, part I and II are specified as general (applicable to all 9 categories of medicines) while Part III and IV are specified under ‘Data Requirement for Veterinary Allopathic Medicines’ of this guideline.

After Registration of the product, if any change related to registered product is to be made; DRA must be notified along with the supporting documents as specified in this guideline. Only after approval from DRA, the changes can be made.
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Background

The Medicines Act of Kingdom of Bhutan was enacted in 2003 and Bhutan Medicines Rules and Regulations in 2005 with subsequent edition in 2008 and 2012. As per Chapter VI section 16.2 of the Act, “All medicinal products, manufactured, sold, and distributed and imported / exported from Bhutan shall be registered under the provisions of this act.” To facilitate the product registration process, this guideline is drawn up in accordance to the chapter IV of the Bhutan Medicines Rules and Regulation, 2012.

This guideline is developed to guide the pharmaceutical companies or the potential Market Authorization Holder (MAH) certified and authorized by Drug Regulatory Authority (DRA) in the preparation and submission of drug registration applications in the form of a dossier or to make changes to an existing registered medicinal products.

The Authority or the registration committee adopts the principle of “Risk-based Approach” for product dossier evaluation which determines the product evaluation route (Abridge or Full Evaluation route).

The application to register of the medicines can be made by any medicinal product manufacturer within or outside Bhutan, or a local pharmacy licensed firm. However, the applicant should ensure that all of the information given in the application form and supporting documents are true and valid at the time of filing application.

The technical evaluation of the medicinal product dossier is done by the technical committee for registration of the medicinal product as approved by the Bhutan Medicines Board.
The Technical committee approves for registration, the medicines manufactured under internationally recognized Pharmacopoeia while the medicines which are manufactured as per In-house specifications require adequate justification with provision of reference standards for testing.

Scope of this guideline

This Guideline shall apply to following categories of medicines:
1. Human allopathic medicines
2. gSo-ba-rig-pa medicines
3. Veterinary allopathic medicines
4. Biologics and Biotechnology Products
5. Complementary medicines
6. Medical gas
7. Active pharmaceutical ingredients for extemporaneous preparation
8. Antiseptics/skin disinfectants

Out-of Scope:
This guideline does not apply to the following products:
1. Diagnostic agents and test kits;
2. Non-medicated medical and contraceptive devices;
3. Non-medicated bandages, surgical dressings, plaster, dental fillings;
4. Instruments, apparatus, syringes, needles, sutures, catheters;
5. food
Registration Exemption

In accordance with section 5.13 of the Act, and chapter IV section 34 of the regulation, medicines may be exempted from registration requirement in following cases;

1. Importation of any product for the purpose of research.
2. Product Samples for the purpose of registration in a quantity not exceeding the quantity as specified below.
3. Medicinal products which are meant for personal use, the quantity sanction for such products will be in accordance with Chapter VII, section 26 of the Act.
4. All the raw materials which are required for manufacture of the medicinal products by the pharmaceutical manufacturers
5. In Public Health Emergencies as defined by the Board.
6. List of Orphan drugs verified by the Chairman, National Drug/ Veterinary Drug Committee and as approved by the Chairman of the board.
7. Medicinal products imported for named patients as sanctioned by the registered medical practitioners in a government Health and Veterinary centres.
8. List of medicines for temporary medical camps for a duration not more than one month.
9. List of Products not registered or not available in the local market at the time of application but required in a government initiated or approved projects for duration not more than one year.
Procedure for Application for Registration:

The route of product registration is broadly classified under 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 medicine are evaluated by other recognized agencies.

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 respectively.
2. Products which are packed together in combination for a therapeutic regimen (example for the treatment of *Helicobacter Pylori*) will be classified as a Combination Pack Product and shall be registered as a single product.
3. Separate applications should be made in respect of different formulation of same medicinal 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, which may be revised from time to time along with the documents detailed under each category of medicines.
6. After filing the application for registration along with the required documents, the dossier at DRA undergoes 2 stage evaluation viz., General Document Evaluation and Technical Document evaluation.
General Requirements of the Dossiers

The dossier should be:
1. In English or Dzongkha or both
2. Properly bonded
3. In A4 size paper
4. Contain price structure of the medicinal products
5. Be complete as per the specifications detailed in this guideline
6. 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.

Guidance on Classification of Medicine

For convenience of registration, medicines are classified into 9 categories based on indications and target species viz.,
1. Human allopathic medicines: Modern conventional medicines which have therapeutic indications based on clinical research and are used in human.

2. gSo-ba-rig-pa medicines: Traditional medicines recognized by the Bhutan Medical and Health Council which are manufactured using the ingredients and methods as per the gSo-ba-rig-pa text.

3. Veterinary allopathic medicines: Modern conventional medicines which have therapeutic indications based on clinical research and are used in veterinary

4. Biologics and Biotechnology Products: Includes the use of the new genetic tools of recombinant DNA to make new genetically modified organisms or genetic engineering, bioinformatics, transformation, diagnostics and vaccine
technology. Biological products include, but are not limited to, bacterial and viral vaccines, therapeutic serums, antitoxins, human blood components and their derivatives, and certain products produced by means of biotechnology.

5. **Complementary medicines**: Products with therapeutic claims as determined by DRA and are intended to supplement the diet taken by mouth in forms such as pills, capsules, tablets, liquids or powders and not represented as conventional food/sole item of a meal or diet. Products with therapeutic claims which do not fall under Human allopathic, Veterinary allopathic, gSo-ba-rig-pa, Biologics and Biotechnology Products will be considered as complimentary medicine.

**Food Drug Interface**

A. **Food**
3. Contains active ingredient less than 20%
4. The food based ingredient is more than 80%
5. It is not in pharmaceutical dosage form such as capsule, softgel, swallowed whole tablet.

B. **Medicinal Product**
1. A product is considered as drug/medicine if the active ingredient is more than 20%.
2. It is in pharmaceutical dosage form (e.g capsule, softgel, swallowed whole tablet).

6. **Medical gas**: Gas which is of pharmacoepial standard and are used in health institutions for its therapeutic purpose.

7. **Active pharmaceutical ingredients for extemporaneous preparation**: Any substance or mixture of substances used in
the compounding of Extemporaneous preparations for intended therapeutic effect. This when used in the formulation forms an active component to which the therapeutic effect of a product is attributed. This excludes the API used by the pharmaceutical manufacturers.

8. **Antiseptics/skin disinfectants:** Includes any medicated chemical used as an antiseptic or for the purpose of disinfection of skins of human and animal. This excludes the medicated chemicals used on inanimate objects.

9. **General Sale List the** list as defined by the Drug Technical Advisory Committee and Bhutan Medicines Board. The list of such medicines will be made available on [www.dra.gov.bt](http://www.dra.gov.bt).
RECEIPT OF DOSSIERS AND PRODUCT SAMPLE

Accept

Reject

Assign Dossier ID on product sample and dossier; enter details on the Log Book and maintain soft copy

PRE-EVALUATION OF THE DOSSIER

Complete Documents

Inform Applicant

Applicant submits missing documents

FULL EVALUATION OF THE DOSSIER

Evaluation of the Product Sample

Product Profile

Quality Profile

Pharmacological Documents

REGULATORY DECISION
Data Requirements

The document requirement for the registration will be based on the route of evaluation to be followed.

ABRIDGED REGISTRATION

Abridge evaluation shall be applicable to;

a. A product that has been evaluated and approved by at least one of the following referenced drug regulatory agency at the time of submission of application for registration;
   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)

b. Medicinal product including the vaccines which are pre-qualified by WHO, UN, OIE or other UN recognized international organizations.

Data Requirements for Abridged Registration

To consider for an abridged evaluation following documents are required:

A. Documentary evidence to support abridged evaluation:
   1. Official approval letters or equivalent documents (like registration certificate for the said product), from the
referenced drug regulatory authority that certify the registration status of the finished product. The certificate of registration issued by the above referenced DRA must be valid at the time of filing application; OR

2. Proof of pre-qualification approval if the medicine is pre-qualified;

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

B. **Declaration Letter**
Official letter declaring that all aspects of the product’s quality intended for sale in Bhutan are identical as that currently approved by the referenced DRA or prequalified by international organization. This includes, but not limited to, the formulation, site(s) of manufacture, raw materials used, 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. The authorization letter should include the list of products authorized by the manufacturer to the dealer.
2. If the letter has provision of validity, the letter must be valid.
3. The letter has authorization for dealer or regional offices of the principle manufacturer, the authorization should be reflected.

D. **Price Structure**
The price structure should:
   i. Indicate price applicable to the wholesaler, retailer and
the maximum retail price.

ii. Include value indicated either in USD or local Bhutanese currency (Ngultrum).

E. **Product Sample**

a. Samples of finished product submitted for registration shall be taken at random from an actual production batch.

b. Samples submitted must be intact and it must be in final commercial pack with original labels and package inserts.

c. Product sample size may vary depending on the type of packaging used:

   i. Minimum of 1 multi dose container, if packed in multi dose container and if packed in strips/blisters; minimum of 2 boxes but not less than following sample size.

   ii. Tablets, Capsules, suppositories – 50 nos.

   iii. Oral liquid, Small Volume Parenteral including solution and powder for inj., IV fluids (Large Volume Parenterals), Eye/Ear Drops, Cream/ointment/lotion, Transdermal patch/ Oral powders/ inhalation and nasal preparation, etc--at least 5 nos. and must be intact in its primary packaging

   d. Product samples submitted must have a remaining shelf-life of at least two (2) years.

   e. The product sample for the medicines which require cold chain maintenance may be exempted.
F. Specimen of Package, Label and insert

a. Specimen of the original package including package, label and insert must be furnished. This specimen must be same as commercially available specimens.

b. Atleast 3 specimens must be included in the dossier.

c. The product label should contain the following information where possible;
   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. Pharmacopoeial 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

d. If the product is without an outer carton, the inner label should bear all the information that is required.

e. The colour of labels should be differentiated between strengths of products. The label must be made from good quality material.
G. Therapeutic indications-Product Information Summary

The Product Information Summary should be consistent with information provided under Product Information Leaflet. It should include the following:

1. The therapeutic category of pharmacological classification to which the pharmaceutical product belong.
2. Therapeutic indication(s) as claimed in the Product Information leaflet provided or Summary of Product Information Sheet.
3. Dose and directions for use for each indication.
4. Mechanism of Action(s) for the claimed indication. The indication may be already established or proposed, as in case of new indications.
5. List of all the major and common side effects. Side effects specific to the particular drug including newly recognized side effects should be identified.
6. Information on use in pregnancy, breastfeeding and other special group of patients including known contraindications and compatibility of use of the finished product with pregnancy and breastfeeding.
7. Pharmacokinetics profile of the finished product should include following parameters:
   a. Plasma half life ($t_{1/2}$)
   b. Apparent volume of distribution ($V_d$)
   c. Plasma protein binding
   d. Clearance
   e. Extent of metabolism
   f. Mode of excretion
FULL REGISTRATION:

1. Full evaluation route shall be applicable to all the category of medicines which does not full abridged evaluation criteria.

2. The medicines 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.

3. While Part I and II are applicable to all the categories of medicine, part IV is however applicable only to allopathic medicines for Human and animal; and biologic & biotechnology products.

4. The Quality document and pharmacological document required is detailed under each category of medicine while general documents and product profile is common, unless specified.

5. As a guide for compilation of the documents into dossier, a check list is provided as Annexure I to this guideline.
Part I-General Documents

In general following documents are required. If however, the medicine 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.

1. Company profile
The company profile documents should include the detail of the following:
   i. Brief history of company with its detailed address including phone and fax number.
   ii. Brief description of the Organization
   iii. Organization chart
   iv. List of the product category manufactured
   v. 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 name
   vi. State whether the company is manufacturing under loan license or not. If so, include details.

2. Current Good Manufacturing Practices (cGMP) certificate
   cGMP certificate should:
   i. Bear the name of the firm, the date of certification and identity of the issuing authority
   ii. Be valid and should have remaining validity of at least 6 months during the time of submission OR
   iii. 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.
3. **Manufacturing License:**
Manufacturing license should:

i. Bear the name of the firm, the date of certification and identity of the issuing authority

ii. Be valid and should have remaining validity of at least 6 months during the time of submission OR

iii. 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.

iv. Contain the list of products applied for registration.

v. Loan license and contract manufacturing status where applicable must be reflected.

4. **Certificate of the Pharmaceutical Product (CoPP)**

   a. CoPP should:

      i. Bear the date of issue, the name of the product, name of the manufacturer and name of the issuing authority

      ii. Be valid and should have remaining validity of at least 6 months during the time of submission OR

      iii. 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.

      iv. Originate from the country where the product is being manufactured

   b. This certification applies **ONLY** to human allopathic medicines and biologic & biotechnology products.

   c. Where possible, the CoPP should be in the format of the WHO Certification Scheme on the Quality of Pharmaceutical Products.
5. **Letter of Authorization from the manufacturer**

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

i. In case of the dealer being involved, letter of authorization issued by the manufacturer must be submitted.

ii. The authorization letter should include the list of products authorized by the manufacturer to the dealer.

iii. The regional office of the principle manufacturing firm may provide the authorization letter. In such case, the letter of authorization from the principle manufacturer to these offices must be furnished.

6. **Evidence of Free Sale**

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

7. **Price Structure**

The price structure should:

i. Indicate price applicable to the wholesaler, retailer and the maximum retail price.

ii. Include value indicated either in USD or local Bhutanese currency

8. **Letter of Evidence**

The letter of evidence stating that the information content in the dossier is originated from the principle manufacturer must be enclosed.
9. **Product Sample**
   a. Samples of finished product submitted for registration shall be taken at random from an actual production batch.
   b. Samples submitted must be intact and it must be in final commercial pack with original labels and package inserts.
   c. Product sample size may vary depending on the type of packaging used:
      i. Minimum of 1 multi dose container, if packed in multi dose container and if packed in strips/blisters; minimum of 2 boxes but not less than following sample size.
      ii. Tablets, Capsules, suppositories — 50 nos.
      iii. Oral liquid, Small Volume Parenteral including solution and powder for inj., IV fluids (Large Volume Parenterals), Eye/Ear Drops, Cream/ointment/lotion, Transdermal patch/ Oral powders/ inhalation and nasal preparation, etc— at least 5 nos. and must be intact in its primary packaging
      
   d. Product samples submitted must have a remaining shelf-life of at least two (2) years.
   e. The product sample for the medicines which require cold chain maintenance may be exempted.

9. **Specimen of Package, Label and insert**
   a. Specimen of the original package including package, label and insert must be furnished. This specimen must be same as commercially available specimens.
   b. Atleast 3 specimens must be included in the dossier.
   c. The product label should contain the following information where possible;
      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

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

Part II-Product Profile

1. This part of the document will apply to all categories of medicines evaluated via full evaluation route unless specified otherwise
2. The product profile should provide following information on the finished product;
a. Generic or International Non-proprietary name (INN)
b. Brand name or trade name (if applicable)
c. Dosage form
d. Strength of the finished product
e. Reference of the official standards of the finished product (e.g. compendial pharmacopoeias or manufacturer’s in-house specification).
f. 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
g. Description of the organoleptic characteristics of the product, including shape, size, superficial markings for identification purposes, colour, odour, taste, consistency, type of tablet coating, type of capsule, superficial markings for identification purposes, etc.
h. 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.
i. Commercial presentation of packaging and pack size in terms of quantity/weight/volume, etc.

3. In addition following information are required for biologics and biotechnology products:
   a. Qualitative statement describing the physical state of the product (eg. Lyophilized solid, powder, liquid etc)
   b. Statement describing the type of finished product (eg. Live/attenuated, killed/inactivated etc for vaccines).

4. For g.so-rig-pa medicine, g.so-rig-pa name and copy of reference formulary (g.so-rig-pa text) must be furnished.
Data Requirements for Human Allopathic Medicines  
Part III-Quality Profile  

A. Technical documents for raw materials  

1. A complete technical/quality specifications and methods of analysis of all raw materials must be submitted. These shall include all requirements and test methods applied as a routine to every batch. The description of the test methods shall be detailed enough to enable the test to be carried out in an independent laboratory.  

2. The technical/quality specifications of each raw material must be presented in separate lists comprising all test applied with the corresponding requirements or test limits. These specifications shall be dated and signed by a person in charge.  

3. For substances which are subject of an official pharmacopoeia, the current edition of the pharmacopoeia in which the substance(s) is official should be used. United States Pharmacopoeia (USP), British Pharmacopoeia (BP), European Pharmacopoeia (EP), Japanese Pharmacopoeia (JP), and other official pharmacopoeia as recognized by the authority should be used. If the procedure used is different from what is described in an official pharmacopoeia, the technical specification shall not be any less stringent than that of the official pharmacopoeia.  

4. The technical information for ingredients not subject of any pharmacopoeia shall be presented as follows:  
   i. The name of the substance supplemented by any trade or scientific synonyms  
   ii. Detailed information on physical and chemical properties with emphasis on solubility, crystalline form, particle size and state of hydration of state of other crystal solvents, polymorphism,
hygroscopicity, melting point, boiling point, density, viscosity, pKa, oil/water partition coefficient etc.

iii. Detailed description of methods of Identification as used for production of the substance, and in the form of tests which ought to be carried out as a routine matter;

iv. Description of purity tests in relation to the sum total of predictable impurities, especially those which may have a harmful effect and if necessary; those which, having regard to the combination of substances to which the application refers, might adversely affect the stability of the medicinal product or distort analytical results.

B. Certificate of Analysis (CoA) of raw materials

Validated and certified copies of the Certificate of Analysis from the supplier of the raw material(s) or the manufacturer of the finished product should be included in the dossier. The certificate(s) should:

1. Be on a letterhead or other paper that adequately identifies the company manufacturing the raw material(s) or company using the raw material(s)
2. Name of the material to which it refers
3. Be dated with the date of analyses and signed by a authorized person over his/her name
4. State the pharmacopoieial specifications and methods against which and by which the tests are performed.
5. All tests and analyses that involve measurement should be reported as the actual numerical results and not description like “complies” or “pass”.

C. Manufacturing process

Following information with regard to manufacturing process should be submitted:

1. A flow diagram giving the steps of the process and showing where materials enter the process. The critical steps and points
at which process controls, intermediate tests or final product controls are conducted should be identified.

2. A narrative description of the manufacturing process, including packaging that represents the sequence of steps undertaken and the scale of production. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater detail.

3. List of equipments used in the manufacture.

4. Appropriate process parameters should be identified, such as time, temperature, or pH in each critical steps of the process

5. A batch manufacturing formula that includes a list of all components of the dosage form to be used in the manufacturing process, with amounts on a per batch basis and total batch size, including overages, functions and a reference to their quality standards.

6. Detailed aseptic requirements for production of sterile products. This shall include data on how sterilization is carried out and controlled. For aseptically prepared drugs, data must be provided on the microbiological quantity or raw material specification and the property of the filter aid.

D. Analytical method for finished product

Analytical method for finished product should include the following:

1. Technical/quality specification of the finished product.

2. Identification tests and assay method for the quantification of the active ingredients in the finished product including how the data obtained are to be analyzed.

3. Identification and assay of the active ingredient(s) carried out either in a representative sample from the production batch or in a number of dosage-units analyzed individually. Certain tests procedures for general characteristics of a product shall always be included among the tests on the finished product. These tests should, wherever applicable, relate to the control of average...
masses and maximum deviations, to mechanical, physical or microbiological tests, organoleptic characteristics, physical characteristics such as density, pH, refractive index, etc. For each of these characteristics, standards and tolerance limits should be specified.

4. Identification tests and assay of preservatives and antioxidants.

5. Validation information, including experimental data for accuracy, specificity, precision, linearity and reproducibility of the analytical procedures used for testing the finished product.

E. Certificate of Analysis (CoA) of finished product
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 finished product. The Certificate, validated and certified should:

i. Be on a letterhead or other copy that adequately identifies the manufacturer of the product.

ii. Be dated with the date of analyses and signed by an authorized person against the name.

iii. State the specifications and methods against which and by which the tests are performed.

iv. Give all tests and analyses that involve measurement as the actual numerical results and not descriptions like "complies" or "pass".

v. Declare acceptable in case of such document being computer generated.

F. Disintegration and dissolution profile
1. Detailed procedures and methods for determining the disintegration and dissolution characteristics of the finished oral solid dosage forms should include:

a. The exact types of equipments, reagents, chemicals etc used for the test and their reference to compendia pharmacopoeia.
b. The test data listed as numerical values along with the tolerance limits.
c. The raw data for those drugs included in the pharmacopoeia and calculations for those not included.

G. Stability test report
The stability test report should include the following:
1. Reports for both Accelerated Stability Study (Temperature 40±2°C and Relative humidity 70±5%) and Real Time Stability Study (Temperature 30±2°C and Relative humidity 60±5%).
2. Stability study should be continued for the full period to validate the predicted shelf life. Where not available, at least 12 months should be completed in case of on-going real time stability study and letter of commitment for submission of report after the completion of the study should be submitted.
3. The types of studies conducted, protocols used, and the summary of the results of the studies. The summary should include results as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.
4. Results of the stability studies presented in an appropriate format such as tabular, graphical, or narrative.
5. Information on analytical procedures used and validation of these procedures.
6. Information on the stability program inclusive of 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. Parameters studied (e.g. content of active ingredient(s), degradation products(s), pH, appearance, homogeneity of creams/ointments, clarity, dissolution)
   f. Testing intervals
g. Initial values

**H. Package information**

1. A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided.

2. The suitability should be discussed with respect to choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.

3. If the official standards/pharmacopoeia includes requirements concerning the type of material used, it must be documented that these requirements will be complied with (e.g. Glass bottles for parenteral solution). This also applies to materials for accessories (infusion sets, syringes, measuring devices).

4. Complete composition, including possible polymerization residues, stabilizers, plasticizers, colouring agents etc., shall be stated. The maximum permitted content shall be indicated. A report on toxicity may be required. Technical properties of the material relevant to the proposed use shall be stated (sterilizability, permeability, transparency, resistance etc.)

5. Detailed information is required about the technical construction of non-standardized containers, e.g. aerosol containers, spray packs, syringes etc.

**I. Certificate of Analysis (CoA) of package and label**

Certificate of quality control test on package and label must be provided from the manufacturer of the package/label or the manufacturer of finished product. CoA shall provide the numerical data on the physical and chemical characteristics of
package and label where possible. Printed labels should be subjected to visual check and should meet the requirements.

Part IV--Pharmacological Documents

A. Product Information Summary
The Product Information Summary should be consistent with information provided under Product Information Leaflet. It should include the following:

1. The therapeutic category of pharmacological classification to which the pharmaceutical product belong.
2. List of indications and dosage as per the requirement given below:
   a. Therapeutic indication(s) as claimed in the Product Information leaflet provided or Summary of Product Information Sheet.
   b. Dose and directions for use for each indication.
3. Mechanism of Action(s) for the claimed indication. The indication may be already established or proposed, as in case of new indications.
4. List of all the major and common side effects. Side effects specific to the particular drug including newly recognized side effects should be identified.
5. Information on use in pregnancy, breastfeeding and other special group of patients including known contraindications and compatibility of use of the finished product with pregnancy and breastfeeding.
6. Pharmacokinetics profile of the finished product should include following parameters:
   a. Plasma half life ($t_{1/2}$)
   b. Apparent volume of distribution ($V_d$)
   c. Plasma protein binding
   d. Clearance
   e. Extent of metabolism
   f. Mode of excretion
B. Bioequivalence (BE) Study Report

Bioavailability (BA) studies are necessary to determine the rate and extent to which the active drug ingredient reaches the target site(s) of action after absorption from a drug formulation.

Bioequivalence utilizes the concept of bioavailability in assessing the comparability of finished products containing the same amount of active ingredients but produced by different manufacturers. Following criteria will be used by the authority in drawing the list of products requiring Bioequivalence studies data:

1. Oral immediate release pharmaceutical products with systemic action when one or more of the following criteria apply:
   a. critical use medicines;
   b. narrow therapeutic range (efficacy/safety margins)
   c. Active pharmaceutical ingredients with bioavailability problems or bio-inequivalence including polymorphs of API, the excipients or the pharmaceutical processes used in manufacturing that could affect the bioequivalence.

2. Modified release pharmaceutical products designed to act by systemic absorption.
3. Fixed combination products with systemic action, where at least one of the active pharmaceutical ingredients requires an in vivo study.

The report of a BE study should include the complete documentation of its protocol, conduct and evaluation in compliance with GCP and WHO Guideline on Registration Requirement to Establish Interchangeability. Following are some of the information that should be included in the report:
   a. Curriculum vitae of the Principal Investigator
b. Approval letter(s) from the Institutional Review Board/Independent Ethics Committee and the appropriate drug regulatory agency wherever the studies is conducted;

c. Information about the reference and test products, including the product name, strength, dosage form, batch number and manufacturer;

d. Certificates of Analysis of the reference and test products used in the BE study;

e. Study protocol

f. Criteria for selection of subjects

g. Selection of dose and sampling time,

h. Description of parameters to be assessed;

i. Description of the assay methodology and validation;

j. Statistical analysis and acceptance ranges

Following categories of medicines if presented as tablets or capsules, either as single ingredient or in combination will require Bio-equivalence studies:

1. Antibiotics
2. Antiviral drugs
3. Antileprosy Drugs
4. Antituberculosis Drugs
5. Antimalarial drugs
6. Antifungal Drugs
7. Antiprotozoal drugs
8. Antineoplastic
9. Immunosuppressive drugs
10. Antianginal drugs
11. Antiarrhythmic drugs
12. Antihypertensive drugs and Diuretics
13. Drugs used in heart failure
14. Steroids
15. Anti-diabetic agents
16. Anti-psychotic drugs
The list of categories for which bioequivalence studies is required is subject to change as deemed necessary by the Authority. In such case, the list will be notified through official website of the Authority.

**Comparative Dissolution study Report**
1. Comparative dissolution study can be used as a substitute for in-vivo pharmacokinetic bioequivalence studies compatible with justification for biowaiver provided.
2. Biopharmaceutics Classification System (BCS) should be used as the main tool for qualification of biowaiver on the basis of dissolution profiles properties of active pharmaceutical ingredient.
3. Biowaiver based on dose proportionality will be considered for approval of different strengths of a generic product on the basis of dissolution profiles, if the formulations have proportionally similar compositions.
4. Approval of generic formulations using comparative *in vitro* dissolution studies should be based on generation of comparative dissolution profiles rather than a single point dissolution test.
5. The dissolution profile of the generic and test products should be made under the same test conditions using an apparatus that conforms to the USP and BP specifications using either the paddle method at 75 rpm or the basket method at 100 rpm in pH 1.2, 4.5 and 6.8 buffers at 37°C. Similarity factor should be used to compare dissolution profiles.

C. **Pre-clinical & Clinical Studies Data**
This data will be REQUIRED ONLY FOR REGISTRATION OF NEWLY INTRODUCED DRUGS as qualified by the authority.

I. Pre-clinical Data

Pre-clinical studies shall include pharmacodynamics, pharmacokinetics, and toxicity studies of the drug.

1. Pharmacodynamics

Pharmacodynamic data should demonstrate the primary pharmacologic effect of the drug leading to its development for the indication(s) intended and other effect it produces on the various systems of the body. Structure Activity Relationship should be used to elucidate the correlation of the actions and effects of drugs with their chemical structures.

2. Pharmacokinetics

Pharmacokinetic data furnished should demonstrate the following:

a. Bioavailability (AUC) to determine the rate and extent of absorption of the drug;

b. Distribution pattern including determination of compartmental model the drug follows and apparent volume of distribution (Vd)

c. Extent of metabolism and metabolic pathway of the drug and its metabolites

d. Route of elimination of the drug and its principal metabolites

e. Plasma half-life ($t_{1/2}$)

f. Clearance from the plasma (Cl).

3. Toxicity data

Toxicity data shall include results of acute toxicity, subchronic and chronic studies done on different species of animals.

a. Acute Toxicity

Acute toxicity data shall show the median lethal dose of a drug. The following parameters should be established:
i. Lethal dose 50 (LD$_{50}$)
ii. Effective dose 50 (ED$_{50}$)
iii. Therapeutic index
iv. No observable adverse effect level (NOEL)
v. Toxidrome

b. Subchronic Toxicity
The subchronic toxicity data shall cover adverse effects from repeated exposures to a chemical over a period of time, the cumulative toxicity and the development of tolerance in target organ with continuous exposure. The parameters used for objective evaluation of drug effects in animals are as follows:

i. Physiologic changes such as body weight, food and water consumption, grooming, bowel movement and urination, temperature, heart rate and respiratory rate.
ii. Hematologic such as Hemoglobin, Hematocrit, White Blood Cells, platelet and reticulocyte count
iii. Liver and renal function tests
iv. Blood sugar and lipid profile
v. Urinalysis
vi. Neurological
vii. Behavioral
viii. Post-mortem analysis

c. Chronic Toxicity
Chronic toxicity studies are useful in determining effects after prolonged exposure which neither acute nor subchronic toxicity study can provide. The parameters to be observed are the same as in subchronic studies.

d. Special Toxicity Data
Special toxicity studies in animals should cover studies of allergenicity; teratogenicity; mutagenicity and carcinogenicity;
effects of the drug on reproduction and the effects on the infants during lactation;

II. Clinical Data
Following documents should be submitted:

a. Certification of the clinical protocol by the Institutional Review Board (IRB) or any other relevant board responsible for approval and monitoring of clinical trial.

b. Clinical Drug Trial data
   i. Phase I
   ii. Phase II Clinical
   iii. Phase III Clinical
   iv. Bioavailability studies

c. Name(s) of investigator(s) and their curriculum vitae

d. Name(s) of center/institution wherein the clinical investigation was undertaken

e. Protocol for Clinical Trial
Data Requirement for g.So-ba-Rig-Pa Medicines
Part III - Quality Profile

A. Technical documents on raw materials
List of raw materials (both active & inactive) shall include information such as botanical names, part used and Family. The specifications both for active and inactive raw materials should include the parameters with defined test limits against each parameter. However, a separate specification may not be required if it is included in the Certificate of Analysis of individual raw materials. The parameters should include the following but not limited to:
1. Part Used
2. Description (Organoleptic characteristics, such as taste, color, odor etc.)
3. Identification test
4. Loss on Drying/Moisture Content as applicable
5. Essential/Volatile oil content as applicable
6. Foreign matters

B. Substitutes for raw materials and their References
Wherever raw material substitute is used; be it for plant, animal and mineral origins, it should be clearly stated in the substitute list against each raw material used. The copies of g.so-ba-rig-pa text references shall be required for the respective substitutes where such similar indications are specified.

C. Certificate of Analysis (CoA) for Raw Materials
1. Validated and certified copies of the Certificate of Analysis from the supplier of the raw material(s) or the manufacturer of the finished product should be included in the dossier.
2. The certificate(s) shall:
   a. Be on a letterhead or other paper that adequately identifies the company manufacturing the raw material(s)
b. Name of the material to which it refers and identify it by a batch number.

c. The batch number of the raw material used in the manufacture of the sample submitted for analyses.

d. Be dated with the date of analyses and signed by an authorized personnel over his/her name.

e. State the specifications and methods against which and by which the tests are performed.

f. All tests and analyses that involve measurement should be reported as the actual numerical results and not description like “complies” or “pass”. Descriptive result such as complies is used only for qualitative test.

D. Information on pre-processed raw materials

Wherever raw materials are pre-processed ex. skya-sgog, the following documents should be included;

1. Specifications including visual photo documentation and presence of any foreign particles and other quality indicating test parameters.


3. A copy of preprocessing method from g.so-rig-pa text if available or a copy of method used.

E. Formulary for a finished product

1. The formulary of a product should:
   a. Enlist the detail of ingredient names in g.so-ba-rig-pa along with the botanical nomenclature,
   b. Include standard ratio of each ingredients in the formulation,
   c. Standard quantity for 1 kg including other additives included in the formulation.

2. A copy of formulary from the g.So-ba-rig-pa text reference is required including indications for respective product
formulary. Where substitutes for and preprocessing of raw materials are required, such requirements should be clearly specified in their respective product formularies against those raw materials.

F. Batch Manufacturing Formula
The Batch Manufacturing Formula should include following information:

- Product name,
- Batch number
- Batch Size,
- Dosage form and strength,
- Actual quantity of raw materials issued per batch size besides other information as included in the formulary.

G. Manufacturing Process
Manufacturing methods for manufacturing process should be provided stepwise in sequential order. Flow chart of manufacturing steps and monitoring of in process quality control conducted during manufacturing process such as uniformity of weight, percent of extract and sugar concentration etc. should be included.

H. Analytical method for finished product
Analytical method for finished product should include the following:

1. Technical/quality specification of the finished product.
2. Identification tests and assay method (where applicable).
3. Certain tests procedures for general characteristics of a product including control of average masses and maximum deviations, to mechanical, physical or organoleptic characteristics; physical characteristics such as density, pH; identification test, Loss on Drying, moisture content;
Disintegration profile; uniformity of weight, assay, etc. For each of these characteristics, standards and tolerance limits should be specified.

4. Microbiological test reports where applicable.

I. Certificate of Analysis (CoA) of finished product
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 finished product. The certified certificate should:
1. Be on a letterhead or other copy that adequately identifies the manufacturer of the product.
2. Be dated with the date of analyses and signed by an authorized person against the name.
3. State the specifications and methods against which and by which the tests are performed.
4. Include result for disintegration studies, where applicable
5. Give all tests and analyses that involve measurement as the actual numerical results and not descriptions like "complies" or "pass". Descriptive result such as complies is used only for qualitative test.

J. Stability Studies
Long term stability studies reports of at least three batches of a product should be submitted in tabular formats. Reports should be signed with dated signature of an analyst. The following information should be provided to support stability studies reports for established shelf life of a product;
1. Storage Conditions 30 ± 2°C and Relative humidity of 65 ± 5%
2. Test parameters (Organoleptic characteristic like color, taste and odor, disintegration profile, and others)
3. Thin Layer Chromatography Profile and Assay if applicable.
4. Container/closure system
5. Testing intervals
6. Initial values
In the event of lack of long term stability studies reports, accelerated studies reports conducted at the storage conditions of 40± 2°C and 75± 5%.

K. Certificate of Analysis (CoA) of package and label
Certificate of quality control test on package and label must be provided from the manufacturer of the package/label or the manufacturer of finished product. CoA shall provide the numerical data on the physical and chemical characteristics of package and label where possible.
Data Requirement for Veterinary Allopathic Medicines

Part III- Quality Profile

A. Technical documents for raw material
1. Technical specification should be provided for all the raw materials including excipients.
2. A complete method of analysis of active pharmaceutical ingredient must be submitted. The quality specifications claimed should be those which are applied by the manufacturer in his own control procedures.
3. Analytical validation information for the analytical procedures used for testing the drug substance should be provided.
4. If the procedure used is different from what is described in an official pharmacopoeia, the technical specification shall not be any less stringent than that of the official pharmacopoeia.

B. Certificate of Analysis (CoA) of Active Pharmaceutical ingredient
Validated and certified copies of the Certificate of Analysis from the supplier of the API or the manufacturer of the finished product should be included in the dossier. The certificate(s) shall:
1. Be on a letterhead or other paper that adequately identifies the company manufacturing the raw material(s) or the finished product
2. Name of the material to which it refers and identify it by a batch number.
3. The batch number of the raw material used in the manufacture of the sample submitted for analyses
4. Be dated with the date of analyses and signed by an authorized person over his/her name
5. State the pharmacopoieal specifications and methods against which and by which the tests are performed.
6. All tests and analyses that involve measurement should be reported as the actual numerical results and not description like “complies” or “pass”.

C. Manufacturing process
Following information with regard to manufacturing process should be submitted:
1. Full description of manufacturing process with flow chart
2. Description of the type of equipment
3. A batch manufacturing formula that includes a list of all components of the dosage form to be used in the manufacturing process, with amounts on a per batch basis and total batch size, including overages, functions and a reference to their quality standards.
4. Detailed aseptic requirements for production of sterile products. This shall include data on how sterilization is carried out and controlled.

D. Analytical method for finished product
Analytical method for finished product should include the following:
1. Technical/quality specification of the finished product.
2. Identification tests and assay method for the quantification of the active ingredients in the finished product including how the data obtained are to be analyzed.
3. Identification and assay of the active ingredient(s) carried out either in a representative sample from the production batch or in a number of dosage-units analyzed individually. Certain tests procedures for general characteristics of a product shall always be included among the tests on the finished product.
These tests should, wherever applicable, relate to the control of average masses and maximum deviations, to mechanical, physical or microbiological tests, organoleptic characteristics, physical characteristics such as density, pH, refractive index, etc. For each of these characteristics, standards and tolerance limits should be specified.

4. Validation information, including experimental data for accuracy, specificity, precision, linearity and reproducibility of the analytical procedures used for testing the finished product.

E. **Certificate of Analysis (CoA) of finished product**

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. The Certificate, validated and certified should:

1. Be on a letterhead or other copy that adequately identifies the manufacturer of the product.
2. Be dated with the date of analyses and signed by an authorized person against the name.
3. State the specifications and methods against which and by which the tests are performed.
4. Include results for disintegration and dissolution, where applicable.
5. Give all tests and analyses that involve measurement as the actual numerical results and not descriptions like "complies" or "pass".

F. **Stability test report**

1. Reports for both Accelerated Stability Study (Temperature 40±2°C and Relative humidity 70±5%) and Real Time Stability Study (Temperature 30±2°C and Relative humidity 60±5%).
2. Stability study should be continued for the full period to validate the predicted shelf life. Where not available, at least 12 months should be completed in case of on-going real time
stability study and letter of commitment for submission of report after the completion of the study should be submitted.

3. Results of the stability studies presented in an appropriate format such as tabular, graphical, or narrative.

4. Information on the stability program inclusive of 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. Parameters studied (e.g. content of active ingredient(s), degradation products(s), pH, appearance, homogeneity of creams/ointments, clarity, dissolution)
   f. Testing intervals
   g. Initial values

5. In addition to the specific stability tests that are required in general following requirements for specific veterinary chemical product types will apply:
   a. **Controlled release dosage forms**: dissolution test
   b. **Intra-mammary products**: test of sterility
   c. Veterinary liquid products for cutaneous application: **stability data** on diluted dipping /jetting and teat spray products

G. **Certificate of analysis (CoA) for package and label**

Report on packaging should include the following:

1. Description of the container closure system including pack size, fill details, container type, etc. For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided.

2. Composition of the construction materials of each primary packaging component
3. Compatibility study of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.

**Part IV-Pharmacological Data**

A. **Product Information Summary**
   The Product Information Summary should be consistent with information provided under Product Information Leaflet. It should include the following:
   1. The therapeutic category of pharmacological classification to which the pharmaceutical product belong.
   2. List of indications and dosage as given below:
      i. Therapeutic indication(s) as claimed in the Product Information leaflet provided
      ii. Dose and directions for use for each indication.
   3. Mechanism of Action(s) for the claimed indication. The indication may be already established or proposed, as in case of new indications.
   4. List of all the major and common side effects. Side effects specific to the particular drug including newly recognized side effects should be identified.
   5. Information on use in pregnancy, lactating animals and other special group of patients including known contraindications and compatibility with pregnancy and lactating animals and laying birds.
      i. Pharmacokinetics profile of the finished product should include following parameters:
      ii. Bioavailability (AUC) studies
      iii. Plasma half life (t_{1/2})
      iv. Distribution pattern
      v. Extent of metabolism and the metabolic pathway (inter species comparison)
vi. Mode of excretion
vii. Clearance

6. **Maximum Allowable Residual Limit (MRL)** for a product intended for human food producing animal species. MRL should be within the acceptable range as acceptable to the referenced DRA of the Authority. Withdrawal period should be indicated in days except for milk withdrawal periods.

**B. Pre-clinical & Clinical Studies Data**

This data will be **REQUIRED ONLY FOR REGISTRATION OF NEWLY INTRODUCED DRUGS** as qualified by the authority.

1. **Pre-clinical Data**
   Pre-clinical studies shall include following:
   a. Pharmacodynamics including structure activity relationship
   b. Pharmacokinetics
   c. Toxicology studies including single dose and repeat dose toxicity, species tolerance, teratogenicity, mutagenicity, carcinogenicity and user safety.

2. **Clinical Data**
   a. Dose determination/ confirmation studies
   b. Clinical trials (tabular presentation of all clinical trials and studies etc)
Data Requirement for Biologics and Biotechnology Products
Part III-Quality Profile

A. Technical documents on raw materials
A list of all materials including bioactive substance and their tests and specifications or reference to official compendia shall be provided. The specification of the raw material should include the following:
1. Name of the raw material
2. Reference of the drug to pharmacopoeial standards or manufacturer’s in-house specification
3. Source or method of production of bioactive substance (strain of microorganism, cell substrate or DNA recombinant technology)
4. A qualitative statement describing the physical state (lyophilized solid, powder, liquid) and colour and clarity of the active ingredient and other ingredients

Quality control method of analysis for raw materials should include following information:

i. A description of method of analysis of bioactive substance and other ingredients.

ii. Analytical validation information for the analytical procedures used for testing the drug substance.

iii. If the procedure used is different from what is described in an official pharmacopoeia, the technical specification shall not be any less stringent than that of the official pharmacopoeia.

B. 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. The certificate(s) shall:
1. Be on a letterhead or other paper that adequately identifies the company manufacturing the raw material(s)
2. Name of the material to which it refers and identify it by a batch number.
3. The batch number of the raw material used in the manufacture of the sample submitted for analyses
4. Be dated with the date of analyses and signed by an authorized person over his/her name
5. State the pharmacopoieal specifications and methods against which and by which the tests are performed.
6. All tests and analyses that involve measurement should be reported as the actual numerical results and not description like “complies” or “pass”.
7. Results of tests for bioactive substance should include specific tests for identity, potency, purity, endotoxin and sterility. In case of the source of bioactive substance being animal or human, specific results for tests including Bovine Spongiform Encephalopathy (BSE), Transmissible Spongiform Encephalopathy (TSE), Hepatitis B, HIV, etc should be submitted.

C. **Manufacturing Process**

Manufacturing process should include the following:
1. A complete visual representation of the manufacturing process flow showing the steps in production, equipment and materials used
2. Appropriate process parameters should be identified, such as time, temperature, or pH in each critical steps of the process
3. A detailed description of the manufacturing and controls to demonstrate proper quality control and prevention of possible contamination.
D. Analytical method for finished product
Analytical method for finished product should include the following:
2. 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.
3. Identification tests and assay of preservatives and antioxidants.
4. Validation information, including experimental data for accuracy, specificity, precision, linearity and reproducibility of the analytical procedures used for testing the finished product.

E. Certificate of Analysis (CoA) of finished product
1. 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 shall be provided.
2. The Certificate, validated and certified should:
   i. Be on a letterhead or other copy that adequately identifies the manufacturer of the product.
   ii. Be dated with the date of analyses and signed by a authorized person against the name.
   iii. State the specifications and methods against which and by which the tests are performed.
   iv. Give all tests and analyses that involve measurement as the actual numerical results and not descriptions like "complies" or "pass".
   v. Declare acceptable in case of such document being computer generated.
F. Stability test report
The stability test report should include the following:
1. Reports for both Accelerated Stability Study (Temperature 40±2°C and Relative humidity 70±5%) and Real Time Stability Study (Temperature 30±2°C and Relative humidity 60±5%).
2. The types of studies conducted, protocols used, and the summary of the results of the studies. The summary should include results as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.
3. Results of the stability studies presented in an appropriate format such as tabular, graphical, or narrative.
4. Information on the stability program inclusive of 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

G. Certificate of Analysis (CoA) for Package and Label
Report should include the following:
1. Description of the container closure system including pack size, fill details, container type, etc. For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided.
2. Composition of the construction materials of each primary packaging component
3. Compatibility study of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.
Part IV-Pharmacological Documents

Product Information Summary
1. The Product Information Summary should be consistent with information provided under Product Information Leaflet. It should include the following:
2. List of indications and dosage as per the requirement given below:
   a. Therapeutic indication(s) as claimed in the Product Information leaflet provided or Summary of Product Information Sheet.
   b. Dose and directions for use for each indication.
   c. Target animal and age group
3. List of all the major and common side effects. Side effects specific to the particular drug including newly recognized side effects should be identified.
4. Information on use in pregnancy, breastfeeding and other special group of patients including known contraindications and compatibility of use of the finished product with pregnancy and breastfeeding.
5. Pharmacokinetics profile of the product.

Data on Biosimilars
The Biologics applied for registration should be biosimilar with the reference product. To establish biosimilarity, at least following documents must be submitted:
1. Data on quality profile including:
   a. Comparative test between reference product and the product applied for registration;
   b. Analytical methods to detect the differences;
   c. Validated comparability studies and characterization studies;
   d. Comparative stability studies.
2. Pharmacology profile including the comparability studies with reference product in terms of:
   a. Suitability of animal models;
   b. *In-vivo* and *in-vitro* Pharmacodynamic and Pharmacokinetic data;
   c. Repeat-dose toxicity;
   d. Evidence of confirmatory to Pharmacodynamic and Pharmacokinetic data;
   e. Clinical efficacy;
   f. Clinical safety and immunogenicity.
Data Requirement for Complementary Medicines
Part III- Quality Profile

A. Batch formula
A batch formula should:
   i. Be provided on an official letterhead of the manufacturer signed by an authorized personnel
   ii. Include the list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis and total batch size

B. Information on ingredients used
Ingredients used in the formulation should be in compliance with following conditions:
   i. It should be included in the list of ingredients allowed in health supplements of referenced DRA
   ii. Ingredients used should not be restricted or banned

C. Manufacturing process
A brief description of manufacturing process including flow diagram should be included.

D. Certificate of Analysis (CoA) of finished product
1. Finished product CoA should give details of quality control specifications including a list of tests and state the limits of acceptance.
2. Reference of each test method must be stated
3. Results must meet the specification and should be expressed as numerical value and not “complies” or “pass”.
4. The CoA must be inclusive of the finished product specification
5. The following are considered critical for products containing ingredients derived from various sources:
   i. Marine source: CoA for dioxin level
Registration Guideline for Registration of the Medicinal Products, 2013

ii. Bovine source: BSE/TSE free certificate from relevant authority

iii. Placenta product: CoA for proof of hormone-free

iv. Aphanizomenon flos-aquae: CoA for the microcystin-LR or total microcystins content

6. Disintegration profile and dissolution characteristic of the product must be provided where applicable. The test result must be reported as a numerical value along with the tolerance limits.
Data Requirements for Medical Gases
Part III- Quality Profile

A. Technical documents for starting material
1. Technical specification should be provided for the starting material and bulk medical gas used in manufacture of medical gas including:
   i. Name.
   ii. Chemical formula.
   iii. Internal code reference if any.
2. The detailed methods for the sampling and testing of the starting materials, including any specified analytical procedures and equipment
   i. The qualitative and quantitative testing requirements of the starting materials with the acceptance limits.
   ii. The storage conditions and precautions.
   iii. The maximum period of storage before re-examination.

B. Manufacturing process
Following information with regard to manufacturing process should be submitted:
   i. A flow diagram giving the steps of the process and showing where materials enter the process.
   ii. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.
   iii. A brief description of the manufacturing process.
   iv. Appropriate process parameters identified, such as time, temperature, pressure and pH in each critical steps of the process and acceptance criteria for such tests.
   v. Batch size
C. **Equipment design and Size**

Equipment must be designed to assure that the proper gas is put into the correct container. Evidence should be furnished to ensure that following elements of design are being considered:

i. The medical gases used are dedicated to a single gas. For mixtures of two or more gases, the mixture is produced by filling the cylinders on manifolds dedicated to mixtures.

ii. The medical gases are equipped with fill connections that correspond only to the container valve connection for that particular gas or mixture of gases so that the wrong containers cannot be attached to the other.

iii. Filling of medical gases containers (concurrently) on the same line is acceptable, provided that the gas used for industrial purposes is equal to or higher in quality than the medical gas.

D. **Specifications for finished product**

Specifications for finished medical gas should include:

i. Name of the product

ii. Chemical formulae and the concentration of each component, where appropriate

iii. Description of the dosage form, whether compressed or liquefied

iv. Relevant details of the gas cylinder, cryogenic container and the outlet valve

E. **Analytical method for finished product**

Analytical method for finished product should include detailed methods for the sampling and testing of the finished product, including the specified analytical procedures for following tests, where applicable:

1. Particulate matter test
2. Gas identity test for identity and quality
3. Oxidisable Substances test
Registration Guideline for Registration of the Medicinal Products, 2013

4. Water test to identify contamination of the pipeline system by moisture. Carbon dioxide test
5. Carbon monoxide test
6. Other test as determined by the pharmaepias

F. Certificate of Analysis (CoA) of finished product

The Certificate, validated and certified should:
1. Be on a letterhead or other copy that adequately identifies the manufacturer of the product.
2. Be dated with the date of analyses and signed by a authorized person against the name.
3. State the specifications and methods against which and by which the tests are performed.
4. Give all tests and analyses that involve measurement as the actual numerical results and not descriptions like "complies" or "pass".

G. Description and specification of the container closure system

1. Description of the container closure system and composition of the construction materials of cylinders should be included.
2. The specification of Cylinder which including maximum load, pressure release, pressure clamp, weight, oil volume release, oil volume clamp, maximum flow, hydraulic oil, viscosity range and temperature range must be submitted.
3. The medical gas cylinder should have the necessary color coding.
Data Requirements for API for Extemporaneous Preparation, Antiseptics and GSL Medicines

Following conditions must be fulfilled to be categorized as Active Pharmaceutical Ingredient (API):
1. Any substance or mixture of substances used in the compounding of Extemporaneous preparations for intended therapeutic effect. This excludes the API used by the pharmaceutical manufacturers;
2. Only the APIs which follows the standard pharmacopeias will be registered

For the medicines to be classified under the category of antiseptics/skin disinfectants and medicines falling under general sale list (GSL), following conditions must be fulfilled:
   a. It should be medicated chemical used as an antiseptic or for the purpose of disinfecting skins of human and animal. This excludes the medicated chemicals used on inanimate objects.
   b. It should be a product falling under GSL as defined by the Drug Technical Advisory Committee and Bhutan Medicines Board. The list of such medicines will be made available on www.dra.gov.bt

Data Requirements
Part III- Quality Profile

A. Manufacturing/Repacking process
Manufacturing process of the product should include following:
1. Procedures and records to indicate that controls are in place to avoid mix-up, contamination and cross contamination.
2. Method to detect the impurities
3. List of solvents or other raw materials used for manufacture or repacking.
B. **Certificate of Analysis (CoA) for finished product**
The CoA should include the results of all the requirements and test methods. The Certificate, validated and certified should:
1. Contain the result of all critical parameters as specified in the Pharmacopoeias
2. Be on a letterhead or other copy that adequately identifies the manufacturer of the product.
3. Be dated with the date of analyses and signed by an authorized person against the name.
4. State the specifications and methods against which and by which the tests are performed.
5. Give all tests and analyses that involve measurement as the actual numerical results and not descriptions like "complies" or "pass".

In addition, where possible CoA issued by the principle manufacturer should be submitted at the time of filing the application.

**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 priority review may be given for treatment of disease conditions that are of local public health concerns. This may include the medicines for cancer, HIV, dengue, tuberculosis, hepatitis and malaria.

3. The request for priority review should be made at the time of
submitting the dossiers along with justification which warrants a priority review. DRA, 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, MAH**

1. The applicant shall be responsible for the product and all information supplied in support of his application for registration of the product.

2. He shall be responsible 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 (cGMP) compliance of the manufacturers.

3. He shall notify the Authority on any changes related to products’ quality, efficacy or safety throughout the product’s life cycle in the country.

4. The MAH must assume responsibility for the quality, safety and efficacy of his/her products.

5. The 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 DRA and approval obtained before import.
Fees for Registration

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

1. **Processing fee:** Every application for registration shall 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 shall 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.

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 shall require separate applications for product registration.
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 the 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 the 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 if:
      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 Registration Committee for Registration of the Medicinal Products. 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 shall 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 shall be valid for a period of three (3) years and shall 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.

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**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 Product Registration

1. Application for renewal shall 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 shall 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 vide abridged evaluation route shall 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 shall be granted with the fulfillment of the following conditions and documents.

7. Condition for renewal

   a. Following mandatory conditions must be fulfilled by the product in question for renewal with minimal documents

      i. There should not be change in the manufacturing site/premise of the particular product;

      ii. There should not be change in the ingredients used for the formulation of the particular product;

      iii. There should not be change in the formulation including colour, size, dosage forms and dosage;
iv. There should not be change in indication and the information on the package insert;

v. There should not be change in the 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

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**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 shall be submitted by the proposed new MAH.

   b. The 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 shall 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 shall 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:
   a. Apply to the Authority in form VIIa-PRC with proposed changes for allopathic medicines and form VIIb-PRC for gSo-ba-Rig-pa medicines.
b. 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:

<table>
<thead>
<tr>
<th>Type of post registration change: Change in product name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditions to be fulfilled</td>
</tr>
<tr>
<td>There is no change to the product (formulation, release and shelf-life specifications, manufacturing source and process etc) except for the product name change.</td>
</tr>
<tr>
<td>Documents to be submitted</td>
</tr>
<tr>
<td>1. Official letter from principle manufacturer requesting for the change of product name</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>3. Revised draft package insert and label incorporating the proposed variation.</td>
</tr>
<tr>
<td>5. Product Sample with proposed name</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of post registration change: Change in the specimen of Package Insert, Patient Information Leaflet, unit carton label, inner label and/or blister strips.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditions to be fulfilled</td>
</tr>
<tr>
<td>Change of the layout/artwork</td>
</tr>
<tr>
<td>Addition/deletion/replacement of pictures, diagrams, bar code, logos and/or texts on the package and label</td>
</tr>
<tr>
<td>Change in information in the insert</td>
</tr>
</tbody>
</table>

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### be fulfilled

(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. Current approved product labeling.
3. Proposed product labeling, a clean and annotated version highlighting the changes made.
4. Letter of declaration from the manufacturer and MAH stating that no other changes on the label except for the intended change.
5. Relevant document/reference to support the changes (where applicable).
6. Product Sample with proposed change

### 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

<table>
<thead>
<tr>
<th>Type of post registration change: Change of outer carton pack sizes for a finished product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditions to be fulfilled</td>
</tr>
<tr>
<td>1. Primary packaging materials remain unchanged.</td>
</tr>
<tr>
<td>2. No other changes except for the change of outer carton pack sizes for a finished product.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Documents to be submitted</th>
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<tbody>
<tr>
<td>1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of post registration change: Change in any part of the (primary) packaging material not in contact with the finished</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>product formulation such as colour of flipoff caps, colour code rings on ampoules</td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Conditions to be fulfilled</td>
</tr>
</tbody>
</table>
| 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 applicable  
                                 | 5. Product sample |

| Type of post registration change: Reduction of shelf-life of the finished product |
|---------------------------------|----------------------------------------------------------------------------------|
| a) As a package for sale and/or | 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. |
| b) After first opening and/or   |                                                                                  |
| c) After dilution/reconstitution|                                                                                  |

| Conditions to be fulfilled     | 1. Results of appropriate real time stability studies covering the duration of proposed |
| Documents to be submitted      |                                                                                     |
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.

<table>
<thead>
<tr>
<th>Type of post registration change: Change of the name or address (for example: postal code, street name) of the manufacturer of finished product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conditions to be fulfilled</strong></td>
</tr>
<tr>
<td>1. The manufacturing site remains the same.</td>
</tr>
<tr>
<td>2. Not applicable to the case in which it involves change in ownership of the manufacturer.</td>
</tr>
<tr>
<td>3. No other changes except for the change of the name and/or address of a manufacturer of the finished product.</td>
</tr>
<tr>
<td><strong>Documents to be submitted</strong></td>
</tr>
<tr>
<td>1. Official letter from the manufacturer requesting for the change in name/address of the plant.</td>
</tr>
<tr>
<td>2. A valid GMP certificate, CoPP which covers the GMP certification or official document from relevant authority confirming the new name and/or address.</td>
</tr>
<tr>
<td>3. Revised drafts of the package insert and labeling incorporating the proposed</td>
</tr>
</tbody>
</table>
Type of post registration change: Change in storage conditions

<table>
<thead>
<tr>
<th>Conditions to be fulfilled</th>
<th>Documents to be submitted</th>
</tr>
</thead>
</table>
| There is no change to the product except for the intended change | 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 |

Type of post registration change: price structure

<table>
<thead>
<tr>
<th>Conditions to be fulfilled</th>
<th>Documents to be submitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no change to the product except for the intended change</td>
<td>Price structure of the product</td>
</tr>
</tbody>
</table>

Type of post registration change: additional indication

<table>
<thead>
<tr>
<th>Conditions to be fulfilled</th>
<th>Documents to be submitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Letter of declaration from the manufacturer and MAH stating that no other changes on the label except for the intended change.</td>
<td>1.</td>
</tr>
</tbody>
</table>
intended change.
2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).
3. Product Sample
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 |

| 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 submitted | 1. Official letter from manufacturer authorizing the change of 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 Pharmacopoeial Standard.
3. Revised draft package, insert and labeling incorporating the proposed change.
5. Price structure, if applicable
6. Product Sample

<table>
<thead>
<tr>
<th>Type of post registration change: Substitution of the raw materials in case of pSo-ba-rig-pa medicines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditions to be fulfilled</td>
</tr>
<tr>
<td>There is no change to the product (formulation, release and shelf-life specifications, manufacturing source and process) except for the substitution of the raw materials</td>
</tr>
<tr>
<td>Documents to be submitted</td>
</tr>
<tr>
<td>1. Justification for change</td>
</tr>
<tr>
<td>2. Official letter from manufacturer authorizing the substitution</td>
</tr>
<tr>
<td>3. A declaration letter from the manufacturer and MAH that there is no other changes to the product/label except for the intended change</td>
</tr>
<tr>
<td>4. Revised draft package, insert and labeling incorporating the proposed change.</td>
</tr>
<tr>
<td>5. Photocopies of gso-ba-rig-pa text references which have such similar therapeutic indications</td>
</tr>
<tr>
<td>6. Price structure, if applicable</td>
</tr>
<tr>
<td>7. Product Sample</td>
</tr>
<tr>
<td>Type of post registration change: Substitution of the specifications for the pre-processed raw materials in case of pSo-ba-rig-pa medicines</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Conditions to be fulfilled</strong></td>
</tr>
</tbody>
</table>
| **Documents to be submitted** | 7. Justification for change  
8. A declaration letter from the manufacturer and MAH that there is no other changes to the product/label except for the intended change.  
9. Test Report on pre-processed raw materials  
10. A copy of preprocessing method from g.so-rig-pa text if available or a copy of method used.  
11. Price structure, if applicable  
12. Product Sample |
Annexure 1: Checklist for Preparation and Submission of the Dossier (Tick if you have included in the Dossier)
Checklist for preparation and submission of the dossier for Full Evaluation route

<table>
<thead>
<tr>
<th>Sl. No Documents</th>
<th>Category of Medicines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Human Allopathic</td>
</tr>
<tr>
<td></td>
<td>Veterinary Allopathic</td>
</tr>
<tr>
<td></td>
<td>pSo-bA-Rig-pa</td>
</tr>
<tr>
<td></td>
<td>Biologics</td>
</tr>
</tbody>
</table>

**Part I- General Documents**

- Company profile
- cGMP Certificate
- Manufacturing License
- CoPP: N/A
- Letter of Authorization from the manufacturer *(if the dealer is involved)*
- Evidence of Free Sale
- Price Structure
- Letter of Evidence
- Product Sample *(Qty as specified by DRA)*
- Specimen of Package including package, label and insert

**Part II- Product profile**

- Product profile

**Part III- Quality profile**

- Technical documents for raw materials including specification, analytical method etc
- Substitutes for raw materials and their References: N/A
- CoA of raw materials: Required only for API

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<table>
<thead>
<tr>
<th>Processed raw materials</th>
<th>N/A</th>
<th>N/A</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulary for a finished product</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Manufacturing process inclusive of Batch Manufacturing Formula</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analytical method for finished product</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoA of finished product</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disintegration and dissolution profile for the finished product (applicable only to tablets and capsules)</td>
<td>Only Disintegration result required</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Stability test report (3 batches)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Package</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product label</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Package insert</td>
<td>Where applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoA of package and label</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Part IV--Pharmacological Documents**

<table>
<thead>
<tr>
<th>Product Information Summary</th>
<th>N/A</th>
<th>N/A</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Allowable Residual Limit (MRL)</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Bioequivalence (BE) Study Report</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Comparative Dissolution study Report</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Data on Biosimilars</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Pre-clinical &amp; Clinical Studies Data</td>
<td>Applicable only to new product</td>
<td>Applicable only to new product</td>
<td>N/A</td>
</tr>
<tr>
<td>Documents</td>
<td>Category of Medicines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complimentary medicines</td>
<td>Medical gas</td>
<td>API, Antiseptics/skin disinfectants and medicines falling under General Sale</td>
</tr>
<tr>
<td><strong>Part I-General Documents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Company profile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cGMP Certificate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacturing License</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter of Authorization from the manufacturer (if the dealer is involved)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence of Free Sale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Price Structure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product Sample</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specimen of Package including package, label and insert</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Part II- Product profile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product profile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Part III-Quality profile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technical documents for starting material</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Equipment design and Size</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Batch formula</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Information on ingredients used</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Manufacturing process</td>
<td></td>
<td></td>
<td>Include repacking procedure, if applicable</td>
</tr>
<tr>
<td>CoA of finished product</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disintegration and dissolution profile</td>
<td>Where applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specifications for finished product</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Checklist for submission and preparation of dossiers that are requested for evaluation via abridged evaluation

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

**NOTE:**
1. N/A: Not Applicable
2. Blank space reflects that the document is required
Annexure 2: Application forms for Registration of the Medicinal Products and related forms
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)
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)

<table>
<thead>
<tr>
<th>Product</th>
<th>Pack</th>
<th>Composition (With Strength)</th>
<th>Manufacturer</th>
</tr>
</thead>
</table>

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:……………………
Date: …………………. Address:………………
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)

<table>
<thead>
<tr>
<th>Product</th>
<th>Pack</th>
<th>Composition (With Strength)</th>
<th>Manufacturer</th>
</tr>
</thead>
</table>

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/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 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: VIIb-PRC
Regulation Section: 44 (a)

APPLICATION FOR POST REGISTRATION CHANGES OF MEDICINES (gSo-ba-rig-pa)

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. substitute for raw materials,
   b. specifications of the product,
   c. pre-processed raw materials,
   d. packaging materials,
   e. label designs,
   f. price structure,
   g. market authorization holder
   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 shall abide by the Medicines Act and Medicines Regulations and any other standards set by the Authority.

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

<table>
<thead>
<tr>
<th>Pack</th>
<th>Composition (With Strength)</th>
<th>Manufacturer</th>
</tr>
</thead>
</table>

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:

We would like to acknowledge the following references:
1. Bhutan Medicines Rules and Regulation 2012
2. Registration Guideline 2006
3. ICH guideline on safety, quality and efficacy of the medicine
4. Drug Registration Guidance document and Veterinary drug registration guidance document, NPCB, Malaysia
5. HSA Registration Guideline a document, Singapore
6. India Registration Guideline
7. Philippines Registration Guideline
8. ASEAN guideline (ACTD)
9. Nigeria Registration guideline
10. Zambia vaccines registration
11. Blue Book, Registration guideline, WHO
12. Evaluation of Biosimilars, WHO
13. PIC/s guideline document
14. WHO guidance on interchangeability
Drug Regulatory Authority:  
*Towards promoting consumers’ confidence in the medicinal products*

**Contact Details:**

Registration Division  
Drug Regulatory Authority  
Royal Government of Bhutan  
Thimphu: Bhutan  
Tel.: +975-02-337076  
EPABX:+975-02-337074(5)  
Fax: +975-02-335803  
www.dra.gov.bt