GUIDELINE FOR REGISTRATION OF MEDICINAL PRODUCTS

2020

DRA-G-D1-RM-01
Version: 02

Registration Division
Drug Regulatory Authority

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Introduction

The Medicines Act of the Kingdom of Bhutan was enacted in 2003 and the Bhutan Medicines Rules and Regulations in 2005 with subsequent editions in 2008, 2012 and 2019. 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 with Chapter IX of the Bhutan Medicines Rules and Regulation, 2019.

This guideline is developed to guide the applicant in the preparation and submission of drug registration applications in the form of a dossier or to make changes to existing registered medicinal products.

The Authority and the Registration Committee for product registration adopts the principle of "Risk-based Approach" for product dossier evaluation which determines the product evaluation route (Full, Abridged and Expedited Registration). This guideline is based on the ASEAN Common Technical Document (CTD) with inclusion of specific requirements for Bhutan.

The application for registration of the medicinal product can be made by any medicinal product manufacturer within or outside Bhutan, a local wholesale pharmacy licensed firm or a government procurement agency. 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 evaluation of the medicinal product dossier is done by the technical committee- Registration Committee for product registration as approved by the Bhutan Medicines Board.

This guideline supersedes the Guideline for Registration of Medicinal Products 2nd edition, 2013. The guideline will be revised from time to time as deemed necessary by the Authority and the Registration Committee for product registration.

Scope

This guideline shall apply to the following categories of medicinal products:

1. Part A: Human Allopathic medicine and API
2. Part B: Veterinary Allopathic medicine and API
3. Part C: Traditional Medicine
4. Part D: Herbal Medicine
5. Part E: APIs for extemporaneous preparation

This Guideline shall not apply to any of the following:

1. Health Supplement
2. Vaccine
3. Biologics and Biotechnology product
4. Medical Device
5. General Sale List and borderline product

References

We would like to acknowledge the following references:

1. ASEAN Common Technical Dossier 2016
2. Bhutan Medicines Rules and Regulation 2019
3. Blue Book, Registration guideline, WHO
4. Drug Registration Guidance document 2019- National Pharmaceutical Regulatory Agency, Ministry of Health, Malaysia
5. Guidance on therapeutic products Registration 2019, Health Sciences Authority, Singapore
6. Guideline for Registration of Medicinal Products 2nd Edition, 2013 – Drug Regulatory Authority, Bhutan.
7. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH guideline on safety, quality and efficacy of the medicine)
8. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH guideline on safety, quality and efficacy of the medicine)
9. Pharmaceutical Inspection Co-operation Scheme (relevant PIC/s guideline)
10. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products, WHO Technical Report Series, No. 1010, 2018. World Health Organization (WHO)
11. The Medicines Act of the Kingdom of Bhutan 2003
12. WHO guidance on interchangeability

Definition of the Terminologies

1. **Abridged Registration route** refers to the route of evaluation of medicinal product which is either prequalified by WHO, OIE, UN recognized international organizations or approved by at least one of the Medicine Regulatory Authority of PIC/s member country at the time of submission of application for registration;
2. **Adverse Drug Reaction (ADR)** refers to any noxious, undesirable, or unintended response to a drug which occurs at therapeutic dose.
3. **Adverse event** refers to 'any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment'.
4. **Authority** refers to the Drug Regulatory Authority, Royal Government of Bhutan.
5. **Drug Product** refers to the dosage form (the finished pharmaceutical product) in the final packaging intended for marketing.
6. **Drug Substance (or Active Pharmaceutical Ingredient- API)** refers to any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in the production of a medicine, becomes an active ingredient of the finished product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.
7. **Drugs Technical Advisory Committee (DTAC)** refers to the committee constituted as per section 5.1 of the Medicines Act of the Kingdom of Bhutan 2003.
8. **Excipient (or inactive ingredient)** refers to any substance other than the drug substance/Active Pharmaceutical Ingredient (API) that is intentionally included in an approved drug delivery system or a finished drug product.
9. **Expedited evaluation route** refers to route of evaluation of product dossier which fulfills the criteria for Expedited registration.
10. **Evaluation** refers to the assessment of the dossier and product sample submitted by the applicant using predefined set of criteria.

11. **Full Evaluation route** refers to the route of evaluation which neither qualifies for Abridged nor Expedited route of registration.
12. **General Document Evaluation** refers to the evaluation of Part I (Administrative and Product Information) and it is only applicable to full route of evaluation.
13. **Good Manufacturing Practices (GMP)** refers to the aspect of quality assurance that ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the product specification.
14. **Herbal medicine** refers to medicine derived from herbal plants and it excludes gSo-ba-rig-pa medicine (traditional medicine).
15. **Impermeable container** refers to container that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions
16. **Market Authorization Holder** refers to the establishment having technical authorization for sale and distribution by wholesale or the product manufacturer or government agency/body.
17. **Maximum Residue Limit (MRL)** refers to the maximum concentration of residue resulting from the use of a veterinary medicinal product (expressed in mg/kg or g/kg on a fresh weight basis) which may be accepted to be legally permitted or recognized as acceptable in or on a food.
18. **Medicinal Product** refers to 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.
19. **Medicine Regulatory Authority** refers to the Drug Regulatory Authority of other country.
20. **National Drug Committee/Veterinary Drug Committee** refers to a committee approved by the Ministry of Health or Ministry of Agriculture and Forests respectively for the purpose of reviewing national drug policy and selection of essential medicines to be used in the government institutional establishments.

21. **Product Dossier** refers to the detail medicinal product profile and technical documents generated from the product manufacturer for the purpose of the registration.
22. **Query** refers to a set of questions/doubts/information requested by the Authority from the applicant.
23. **Registration Committee for product registration** refers to the committee as approved by the Bhutan Medicines Board for evaluation of medicinal product.
24. **Regulation** refers to the Bhutan Medicines Rules and Regulation 2019.
25. **Second Brand** refers to another drug product which is identical to a registered drug product in all aspects of quality, safety and efficacy and is manufactured from the same facility.
26. **Semi–permeable container** refers to containers that allow the passage of solvent, usually water, while preventing solute, e.g, plastic bags, semi-rigid low-density polyethylene (LDPE) pouches for large-volume parenterals and LDPE and high-density polyethylene (HDPE) ampoules, bottles and vials.
27. **Technical Document Evaluation** refers to the evaluation of part II, Part III and Part IV data (in case of FDCs, additional specific data) requirements of the full evaluation and all the documents of the abridged and expedited route of evaluation.
28. **Traditional Medicine** refers to medicines recognized by the Bhutan Medical and Health Council which are manufactured using ingredient(s) and method as per the gSo-ba-rig-pa text for gSo-ba-rig-pa indication.
29. **Withdrawal Period** refers to the minimum period between the last administration of the veterinary product to animals under normal conditions of use and the production of foodstuffs from such animals to ensure that such foodstuffs do not contain residues in quantities in excess of the maximum residue limits.

Abbreviations/Acronyms

ACTD:	ASEAN Common Technical Dossier
ADR:	Adverse Drug Reaction
ASEAN:	Association of South East Asian Nations
API:	Active Pharmaceutical Ingredient
APIs:	Active Pharmaceutical Ingredients
BA:	Bioavailability
BCS:	Biopharmaceutics Classification System
BE:	Bioequivalence
BMRR:	Bhutan Medicine Rules and Regulation 2019
BP:	British Pharmacopoeia
cGMP:	current Good Manufacturing Practices
CoA:	Certificate of Analysis
CoPP:	Certificate of Pharmaceutical Product
CTD:	Common Technical Document
DRA:	Drug Regulatory Authority
DTAC:	Drugs Technical Advisory Committee
EP:	European Pharmacopoeia
FDC:	Fixed Dose Combination
GCP:	Good Clinical Practices
GDA:	Generic Drug Application
GMP:	Good Manufacturing Practices
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INN:	International Non-proprietary name
INR:	Indian Rupee
IP:	Indian Pharmacopoeia
IPQC:	In-process Quality Control
MAH:	Market Authorization Holder
MRL:	Maximum Allowable Residual Limit
MRP:	Maximum Retail Price
NA:	Not Applicable
NCE:	New Chemical Entity
NDA:	New Drug Application
NMT:	Not More Than

MRA:	Medicine Regulatory Authority
OIE:	World Organization for Animal Health
PIC/s:	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PSUR:	Periodic Safety Update Report
QOS:	Quality Overall Summary
RH:	Relative Humidity
TAMC:	Total Aerobic Microbial Count
TSE:	Transmissible Spongiform Encephalopathy
TYMC:	Total Yeast and Mould Count
USD:	United States Dollar
USP:	United States Pharmacopoeia
UN:	United Nations
VICH:	Internal Corporation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WHO:	World Health Organization

General Principles and Requirement for Registration

1. Classification of Medicines

Medicines are classified into following categories:

a. **Human allopathic medicine and API**: Modern conventional medicines/chemicals which have therapeutic indications based on clinical research and are used in human.
b. **Veterinary allopathic medicines and API**: Modern conventional medicines/chemicals which have therapeutic indications based on clinical research and are used in animals.
c. **Traditional medicines**: Medicines recognized by the Bhutan Medical and Health Council which are manufactured using ingredient(s) and method as per the gSo-ba-rig-pa text.
d. **Herbal Medicines** refers to medicine derived from herbal plants and excludes Traditional medicine.
e. **APIs for extemporaneous preparation** refers to APIs for the pharmaceutical preparation by means of compounding for patients.

2. Types of Application

a. The application for registration of medicinal products can be made either as NDA or GDA.

b. An application is considered as NDA if it fulfills any of the following conditions:
   i. the drug product contains a chemical or biological active ingredient which is not registered in any other country.
   ii. the drug product approved for certain claims, which is now proposed to be marketed with new indications, dose, dosage form (including sustained release dosage form) and route of administration.
   iii. FDCs proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed with new indications, dosage, dosage form (including sustained release dosage form) and/or route of administration.

c. An application is considered as GDA if it fulfills any of the following conditions:
   i. the drug product is approved by at least one Medicine Regulatory Authority and it has been marketed in the country of origin for a period of more than two years with adequate evidence on safety of the drug product in published journals/listed in an official compendia

   OR

   ii. The drug product has been registered by the Authority as NDA for a minimum of four years.

d. Documents requirement for registration as NDA are as follows:
   i. Part I-Administrative Data and Product Information;
   ii. Part II- Quality Documents
   iii. Part III-Non-clinical Documents
   iv. Part IV-Clinical Documents

e. Documents requirement for registration as GDA are as follows:
   i. Part I-Administrative Data and Product Information
   ii. Part II- Quality Documents.

f. The application for registration must be accompanied by application fee, which may be revised from time to time along with the documents detailed under each category of medicines.

g. After filing the application for registration, the dossier undergoes two stages of evaluation viz., General Document Evaluation and Technical Document evaluation.

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

i. The second brand for the registered drug product from the same manufacturer may not be accepted for registration unless

there is an emergency in the country as determined by the Authority.

j. The validity of the product registration certificate is for a period of three years from the date of issue.

k. Once the application is cancelled or rejected, it will be processed as a new application.

l. Fixed Dose Combinations

i. An application to register FDC may fall into any one of the following four types:

- Type 1 FDC: The FDC contains the same active ingredients in the same doses as an existing FDC
- Type 2 FDC: The FDC contains the same active ingredients in the same doses as an established regime of single entity products, and the dosage regimen is the same. Alternatively the established regime may involve combinations of single entities and FDCs, for example, a single entity drug product combined with an FDC that contains two active ingredients. In all cases, the established regime has a well-characterized safety and efficacy profile, and all of the drug products used in obtaining clinical evidence have been shown to be of good quality
- Type 3 FDC: The new FDC combines active ingredients that are of established safety and efficacy but have not previously been used in combination for this indication. The new FDC comprises a combination for which safety and efficacy have been established, but that will be used in a different dosage regimen
- Type 4 FDC: The new FDC contains one or more new chemical entities

ii. All the requirements for single entity drug product are applicable in addition to the specific requirements for FDCs as detailed in Annexure 1.

3. Routes of Registration

a. Full Registration:

Applicable for registration as NDA or GDA which is not eligible for abridged or expedited registration.

b. Abridged Registration:

i. A generic drug product may be registered through abridged registration upon fulfillment of any of the following conditions:

- The drug product is prequalified by WHO,UN,OIE or other UN recognized international organizations;

OR

- The drug product is approved by at least one of the Medicine Regulatory Authority of PICs member country at the time of application for registration.

ii. Documents Required for Abridged Registration

- Evidence to support abridged registration;
- Declaration Letter;
- Letter of Authorization;
- Specimen of package, label and insert;
- Product Sample; and
- Price Structure.

c. Expedited Registration:

i. A generic drug product may be registered through expedited registration upon fulfillment of following conditions:

- Minimum of five products registered and imported with approval from the Authority for at least two years with active registration status at the time of application;
- No past record of product recall or withdrawal from Bhutan excluding voluntary recall by the manufacturer; and
- For parenteral products, at least one parenteral product to be registered and imported amongst the five valid products.

OR

- cGMP compliant manufacturer verified from the GMP inspection report of DRA and/or other MRAs wherever applicable.

OR

- Registered by at least two other MRAs.

ii. Documents Required for Expedited Registration

- Evidence of registration in at least two other MRAs where applicable
- Letter of authorization
- Certificate of Analysis of drug product
- Method of analysis of drug product for non-compendia method
- Specimen of package, label and insert
- Product Sample
- Price Structure

4. Cancellation of Registration

The Authority may, in the interest of public safety, reject or cancel the registration of any product and such products shall not be imported, manufactured, sold, supplied or possessed for sale, if:

a. 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 GMP audit.
b. Any reports on adverse drug reactions of serious nature have been received from National Pharmacovigilance Centre or any other national or international sources.
c. MAH defaults timely renewal beyond 30 working days of grace period.
d. Voluntary withdrawal of registration by the MAH.
e. Manufacturer or MAH obstructs the inspection of the Manufacturing firms or premises.

OR

f. For any other matters as specified by the Board at the time of cancellation.

5. Registration Exemption

In accordance with section 5.13 of the Act, and chapter IV section 34 of the Regulation, medicines may be exempted from the registration requirement on the following grounds;

a. Medicinal product for the purpose of research.
b. Product sample for the purpose of registration in a quantity not exceeding five samples.
c. Medicinal product for personal use, in a quantity not exceeding the amount stated in the prescription unless justified by a registered medical practitioner.
d. Limited quantities of medicinal products for specific diseases on named-patient basis.
e. In public health emergencies as notified by relevant agencies.
f. Limited quantities of medicines required for approved medical camps.
g. All the imported raw materials for the manufacture of medicinal products in the country.
h. Products not registered but required in limited quantities for time bound government approved projects.
i. Medicinal products donated to government agencies or international organizations/institutions.

6. General Requirements of the Dossiers

The dossier should be:

a. submitted in hard copy or electronically; and in case of hard copy submission it should be in A4 size, properly bound with pages numbered accurately.
b. complete as per the requirements specified in this guideline;
c. either in English or Dzongkha. For documents in foreign local language, the English translation may be accepted provided it is authenticated by the MRA or Public Notary of the country of origin.
d. submitted as per the ACTD format wherein:
    i. Part I of the dossier should contain documents related to administrative data and the drug product information.
    ii. Part II of the dossier should contain data related to quality of the drug product.

iii. Part III and IV of the dossier should contain data related to nonclinical and clinical studies respectively.

e. Submitted with original manufacturing license/CoPP/cGMP and Free Sale Certificate or in case of duplicate copy it must be attested by the Public Notary.

7. Renewal of Registration

a. The procedure for the renewal will be same as the initial registration.
b. One time renewal shall be granted provided all the specifications of product remains same as registered product.
c. Application for renewal shall be submitted as per Annexure 1 within 90 calendar days before the expiry date of registration along with the processing fee.
d. A grace period of 30 working days 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.
e. Upon the completion of the grace period or failure to provide the evidence of having carried out renewal process, the product registration shall be cancelled.

f. Following documents are required for renewal:
   i. Declaration Letter from the company (stating that there is no change in all aspect of the registered product as per Annexure 6
   ii. A copy of initial registration certificate
   iii. Specimen of package, label and insert
   iv. Product Sample

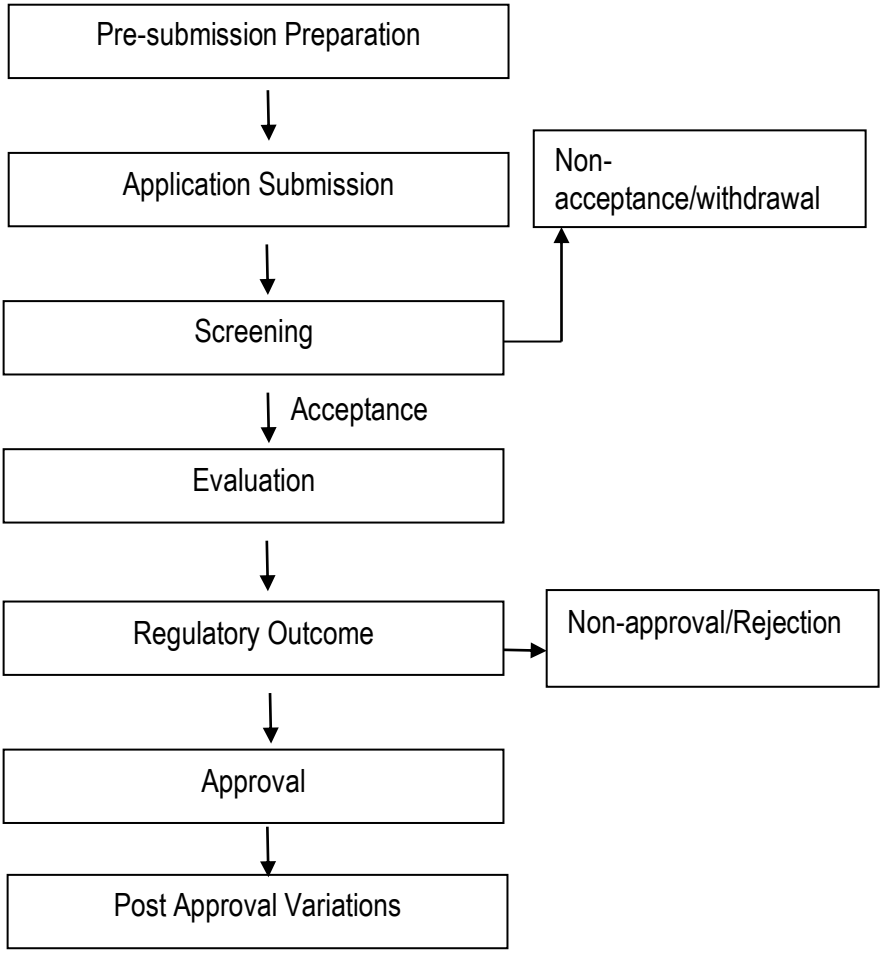
8. Product Registration Transfer

a. An application to transfer the marketing authorization of a product shall be submitted with the prescribed fees.
b. The marketing authorization of the registered product may be transferred if the manufacturer authorizes a new MAH when the

registered product has a remaining validity of at least one month.

c. Following are the documents required for transfer of MAH:
   i. An original letter of authorization from the principle manufacturer to the new MAH specifying the name of the product.
   ii. No Objection Certificate/letter from the current MAH. If without any justifiable reason, the existing market authorization holder denies to give No Objection Certificate/letter within 15 working days, the Authority may approve the transfer based on the letter of authorization from the manufacturer.

9. Process Flow for Registration



10. Procedure for Registration

a. Pre-submission Preparation

The applicant may discuss with the Authority regarding:

i. Type of application
ii. Evaluation route
iii. Document required against respective application type and evaluation routes
iv. Product sample requirement

b. Application Submission

The applicant submits dossier along with prescribed fee and application form as per Annexure 1.

c. Application Screening

i. Following the receipt of the application by the Authority, the dossier will be screened to ensure the correctness of the application type and the completeness of the dossier.

ii. The date of receipt of the application including the checklist will be taken as the submission date and the start of the screening timeline.

iii. The turnaround time for the application screening is 10 working days.

iv. During screening, the application type/evaluation route may be reassigned to a more appropriate one. The applicant will be informed of this change and the Authority will take necessary actions.

v. Applications will not be accepted for the following deficiencies which is not exhaustive to:
   - An entire part of the dossier is not submitted.
   - The dossier contains unexplained information from different manufacturers.

vi. If deficiencies are identified in an application, a screening query will be sent to the applicant.

vii. If the applicant fails to address the deficiencies raised during screening, the application will not be accepted for evaluation.

viii. The stop-clock starts when a query is sent and ends upon receipt of a complete and satisfactory response to the query from the applicant.

ix. The total number of queries sent during screening will be capped at two.

x. An applicant has fifteen (15) working days to respond to each query starting from the date of dispatch of query.

xi. The application will only be accepted when all deficiencies have been adequately addressed and the Authority is satisfied that the dossier is complete for evaluation.

xii. If the application is subsequently re-submitted, it will be processed as a new application.

d. Application Evaluation

i. Once the application is accepted after screening, the evaluation stage begins.

ii. Evaluation queries may be issued to the applicant if clarification or additional information is required. The maximum number of queries from the Authority will be capped at two.

iii. The stop-clock starts whenever the Authority issues a query and stops upon the receipt of a response from the applicant.

iv. The registration certificate will be issued within sixty (60) calendar days from the date of receipt of complete required documents after the application screening;

v. The application shall be rejected if the submitted information in the dossier is completely different against the application made.

vi. The Authority may engage external evaluators, experts and advisory committee in the evaluation process, when deemed necessary. These experts may be included from both local or/and overseas institutions. All external evaluators and experts are bound by conflict of interest and agreement to protect the information made available to them.

vii. The qualification and experience of the evaluators shall be based on the provision of the Quality Manual of the Authority.

e. Rejection of the Application after evaluation

i. An application for registration will be rejected after evaluation if:

- The applicant fails to respond to the queries or submit the required additional documents within six months from the date of last correspondence.
- The applicant fails to submit all the required documents and complete the registration formalities within one (1) year.

ii. If the application is subsequently re-submitted, it will be processed as a new application.

f. Regulatory Outcome

i. A regulatory decision is made following the conclusion of the risk-benefit assessment by the Authority based on the data submitted.

ii. Applicants will be notified of one of the following outcomes:
- ***Approval***: the application satisfies the requirements of registration.
- ***Pending***: the application can be approved subject to adequate response to deficiencies and/or testing reports.
- ***Rejection***: the application does not satisfy the requirements of registration.

g. Post-approval variation

i. The Authority must be notified of any changes to the product's quality, safety and efficacy.

ii. The applicant may apply for any post approval variations during the valid period of registration in form as per Annexure 1.

iii. The data requirement for post approval variation is as per Annexure 4.

SECTION A: HUMAN ALLOPATHIC MEDICINES AND APIs

PART I: ADMINISTRATIVE DATA AND PRODUCT INFORMATION

Administrative Data

1. Site Master File as per the WHO/PIC/s format

2. Current Good Manufacturing Practices (cGMP) certificate

cGMP certificate should:

a. bear the name and address of the manufacturer, the date of certification and identity of the issuing authority
b. be valid and should have remaining validity of at least three months during the time of submission; otherwise an 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

Contract manufacturing license status where applicable must be reflected and technical agreement or certificates should be submitted.

Manufacturing license should:

a. bear the name and address of the manufacturer, the date of certification and identity of the issuing authority
b. be valid and should have remaining validity of at least three months during the time of submission; otherwise an evidence of application or under process letter for renewal of same issued by the licensing authority must be submitted along with the license
c. contain the list of products applied for registration.

4. Certificate of the Pharmaceutical Product (CoPP)

The CoPP issued solely for the export purpose will not be accepted**;** CoPP should:

a. bear the date of issue, the name of the product, manufacturer and details of the issuing authority

b. be valid and have remaining validity of at least three months during the time of submission; otherwise an evidence of application or under process letter for renewal of same issued by the licensing authority must be submitted along with the certificate
c. originate from the country where the product is being manufactured
d. reflect/specify Bhutan as the importing country
e. contains the information as per WHO format.

5. Letter of Authorization

a. The letter of authorization from the manufacturer should be submitted in the specified format as per annexure 3
b. The regional offices of the principal manufacturer may provide letter of authorization. In such cases, the letter of authorization from the principal manufacturer to these offices must be submitted
c. In case of more than one letter of authorization for the same product, the letter of authorization from the principal company shall be considered
d. In case of more than one letter of authorization from equivalent offices of same manufacturer for the same product(s), the initial one shall be considered.

6. Regulatory Status in other countries

Information regarding countries where the drug product is marketed, approved, withdrawn, if any with reasons, restrictions on use, if any.

7. Price

The price should:

a. indicate MRP
b. be indicated either in USD, INR or local Bhutanese currency (Ngultrum)

8. Product Sample

a. One unit pack of product sample from an actual production batch must be submitted at the time of application for registration

b. The product sample may vary depending on the type of packaging used as follows:

   i. Tablet: 10 numbers
   ii. Capsule: 10 numbers
   iii. Pellet: 10 numbers
   iv. Suppository and Pessary: 10 numbers
   v. Semi-solid preparations (creams, ointments, gels, pastes, etc.): 1 unit pack
   vi. IV fluid: 1 unit pack
   vii. Powder: 1 unit pack
   viii. Solution: 1 unit pack
   ix. Spray: 1 unit pack

c. For the purpose of testing, additional sample should be submitted by the MAH at free of cost as per the sample size determined by the testing laboratory and/or as per sampling guideline of the Authority

d. Sample must be intact, in final commercial pack along with product insert/patient information leaflet (where applicable)

e. Sample must have a remaining shelf-life of at least 50% of the claimed shelf-life at the time of submission

f. Controlled drugs or medicines requiring cold chain monitoring may be exempted from submission of sample.

9. Specimen of Package, Label and Insert

a. Specimen of the original package including primary label, secondary label and product insert/patient information leaflet (where applicable) should be submitted

b. The specifications of products available in the market must be the same as the specimen submitted at the time of application for registration

c. The product label should contain the following information:

   i. Product name
   ii. Dosage form

iii. Name and strength of active ingredient(s)/ content of formulation with quantity of ingredients per dosage unit
iv. Batch no.
v. Date of manufacture
vi. Date of expiry
vii. Compendial standard where applicable
viii. Route of administration (where applicable)
ix. Storage conditions
x. Name and address of the manufacturer
xi. Pack size (unit/volume)
xii. Warnings/ cautions/precautionary information (where applicable)
xiii. 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 specimen of the original package including primary label, secondary label and product insert/patient information leaflet must be made from good quality material

f. If the container label is too small for example label of small volume parenteral, not all the above requirements are applicable. The following information must be reflected on such labels:
   i. Product name
   ii. Name and strength of active ingredient(s)
   iii. Lot/batch number;
   iv. Name of the manufacturer, packer, or distributor
   v. Date of expiry

g. A product insert should contain the following information where applicable:
   i. Product Name
   ii. Name and strength of active ingredient (s)
   iii. Product description
   iv. Pharmacodynamics / Pharmacokinetic
   v. Indication

vi. Recommended dose
vii. Mode of administration
viii. Contraindication
ix. Warnings and precautions
x. Drug interactions
xi. Pregnancy and lactation
xii. Undesirable effects
xiii. Overdose and treatment
xiv. Storage condition
xv. Dosage forms and packaging

Product Information

a. The product information should contain the following information on drug product:
    i. Generic or International Nonproprietary name (INN)
    ii. Brand name or trade name (if applicable)
    iii. Dosage form
    iv. Strength
    v. Compendial/ In-house specifications
    vi. 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
    vii. Description of the organoleptic characteristics
    viii. Commercial presentation of packaging and pack size
    ix. The therapeutic category/pharmacological classification to which the pharmaceutical product belongs
    x. Dose and directions for use for each indication
    xi. Mechanism of Action(s) for the claimed indication
    xii. List of all the major and common side effects. Side effects specific to the particular drug including newly recognized side effects should be identified
    xiii. Information on use in pregnancy, breastfeeding and other special group of patients including known contraindications and compatibility of use of the finished product during pregnancy andbreastfeeding

PART II: QUALITY DATA

1. Quality Overall Summary: As per annexure 5

2. Drug Substance and Excipients

a. International non–proprietary name (INN), compendial name if relevant, Laboratory code (if applicable) or chemical name(s) of drug substance and excipients.
b. Physicochemical and other relevant properties of the drug substance.
c. Technical or quality specification of drug substance and excipients.
d. Compendial reference of drug substance and excipients.
e. Certificate of analysis of drug substance and excipients.
f. Name and full addresses including the city and country of the manufacturer of drug substances.
g. For registration of drug product, the document requirement for drug substance is less comprehensive compared to the drug product as the quality of the drug product is considered to establish the quality of its drug substance. However, for the sole purpose of registration of drug substance, the document requirement will be at par with the drug product.

3. Drug Product

a. A description of the drug product and its composition.
b. A copy of monograph for drug product from official compendia shall be submitted for official compendial drug products.
c. Reference test method or a copy of the compendial monograph for the in-house method if the product is tested on the basis of a monograph in an official compendia.
d. Detailed method of analysis including validation process and reports for drug product manufactured using in-house specifications.

4. Manufacturing Process

Contract manufacturing license status where applicable must be reflected and technical agreement or certificates should be submitted.

a. Flow diagram illustrating steps or process involved in manufacturing of the drug product. It should include critical process controls, intermediate tests or final product controls conducted.
b. 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 greater detail.
c. List of equipment used during the manufacture
d. Appropriate process parameters such as time, temperature, or pH in each critical step of the process.
e. 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.

f. Detailed aseptic requirements for production of sterile products. This shall include data on how sterilization is carried out and controlled.
g. Control of critical steps and intermediates in manufacture (IPQC).
h. Analytical procedure used for testing the drug product manufactured using in-house specifications.
i. Validation of analytical procedures used for testing the drug product manufactured using in-house specifications.

5. Certificate of Analysis of Drug Product

All the test parameters specified under compendial monograph and in-house method should be performed where applicable.

6. Container Closure System

a. Description of container closure system including the identity of materials of construction of each primary packaging and secondary package with their specifications.
b. Certificate of analysis of package, label and inserts (where applicable).
c. The suitability of the container closure system used shall be as per WHO Annex 9, WHO Technical report series, No. 902, 2002 and its subsequent updated versions

7. Product Stability

a. Stability study protocol should at least contain:
    i. number of batches and different batch sizes, if applicable
    ii. relevant physical, chemical, microbiological and biological test parameters with acceptance criteria or reference to the attached specifications
    iii. description of the container-closure system
    iv. testing frequency
    v. description of the conditions of storage (standardized conditions for long-term testing and accelerated.)
    vi. results of the stability studies presented in an appropriate format such as tabular, graphical, or narrative.

b. Stability study should be continued for the full period to validate the predicted shelf life.
c. Where not available, the real time stability data at the time of submission should be at least six months for GDA and 12 months for NDA. It should be submitted with letter of commitment for submission of report after the completion of the study.
d. For accelerated stability study, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months) from a six month study is recommended.
e. Reports for both accelerated stability study and real time stability study should be submitted as per the storage conditions specified in table 1.
   The detail guideline on conducting stability study can be referred from Annexure 10, WHO Technical Report Series, No.1010, 2018 or its subsequent versions.

Type of containers/ packaging in which medicinal products are packed	Storage Conditions	
	Long term	Accelerated
General Case and impermeable containers	30°C ± 2°C/75% RH ± 5% RH	40°C ± 2°C/75% RH ± 5% RH
Semi permeable containers	30°C ± 2°C/35% RH ± 5% RH	40°C ± 2°C/not more than (NMT) 25 % RH ± 5% RH
Storage in a refrigerator	5°C ± 3°C	25°C ± 2°C/60% RH ± 5% RH
Storage in a freezer	-20°C ± 5°C	-
Storage below -20°C	case-by-case basis	case-by-case basis

Table 1 Storage Conditions for Stability Study.

8. Product Interchangeability

a. For the product interchangeability of generic drug product, bioequivalence data should be submitted
b. Comparative dissolution study can be used as a substitute for in-vivo bioequivalence studies based on the WHO Biowaiver List as per Annex 8, WHO Technical Report Series, No. 937, 2006 or its subsequent versions
c. The report of a bioequivalence 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
d. Bioequivalence study report should at least include:
    i. Curriculum vitae of the Principal Investigator

ii. Approval letter from the Institutional Review Board or Independent Ethics Committee and the appropriate drug regulatory agency wherever the studies is conducted
iii. Information about the reference and test products, including the product name, strength, dosage form, batch number and manufacturer
iv. Certificates of Analysis of the reference and test products used in the BE study
v. Study protocol
vi. Criteria for selection of subjects
vii. Selection of dose and sampling time,
viii. Description of parameters to be assessed;
ix. Description of the assay methodology and validation;
x. Statistical analysis and acceptance ranges

e. Comparative dissolution study can be used as a substitute for in-vivo pharmacokinetic bioequivalence studies under the condition that genuine justification for biowaiver is provided.
f. 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.
g. The dissolution profile of the generic and test products should be made under the same test conditions using an apparatus that conforms to the compendia specifications.
h. Similarity factor should be used to compare dissolution profiles.

PART III: NON-CLINICAL DOCUMENT

1. Non-clinical document is not required for Generic Products (GDA).

2. For NDA, following documents should be submitted:
    a. Pharmacology
    b. Pharmacokinetics
    c. Toxicology

3. For detailed requirement on the contents of nonclinical documents, refer ICH CTD Guidelines: M4S (Safety) or ACTD part III: Nonclinical Guidelines or any other guidelines recognized by the Authority for this purpose.

PART IV: CLINICAL DOCUMENT

1. Clinical document is not required for Generic Products (GDA).

2. For NDA, following documents should be submitted.
    a. Biopharmaceutics and associated analytical methods
    b. Clinical Pharmacology Studies
    c. Clinical Efficacy
    d. Clinical Safety

3. For detailed requirement on the contents of Clinical documents, refer to ICH CTD Guidelines: M4E (Efficacy) and E3 (Clinical study reports), or ACTD part IV: Clinical Guidelines, or any other guidelines recognized by the Authority for this purpose.

SECTION B: VETERINARY ALLOPATHIC MEDICINES and API

PART I: ADMINISTRATIVE DATA AND PRODUCT INFORMATION

Administrative Data

1. **Site Master File as per the WHO/PICS format**

2. **Current Good Manufacturing Practices (cGMP) certificate**

cGMP certificate should:

a. bear the name and address of the manufacturer, the date of certification and identity of the issuing authority
b. be valid and should have remaining validity of at least three months during the time of submission; otherwise an 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:

a. bear the name and address of the manufacturer, the date of certification and identity of the issuing authority
b. be valid and should have remaining validity of at least three months during the time of submission; otherwise an evidence of application or under process letter for renewal of same issued by the licensing authority must be submitted along with the license
c. contain the list of products applied for registration
d. Loan license and contract manufacturing license status where applicable must be reflected and technical agreement or certificates should be submitted.

4. **Letter of Authorization**

a. The letter of authorization from the manufacturer should be submitted in the specified format as per annexure 3
b. The regional offices of the principal manufacturer may provide letter of authorization. In such cases, the letter of

authorization from the principal manufacturer to these offices must be submitted

c. In case of more than one letter of authorization for the same product, the letter of authorization from the principal company shall be considered
d. In case of more than one letter of authorization from equivalent offices, the initial one shall be considered.

5. Regulatory Status in other countries

Information regarding countries where the drug product is marketed, approved, withdrawn, if any with reasons, restrictions on use, if any.

6. Price

The price should:

a. indicate MRP
b. be indicated either in USD, INR or local Bhutanese currency (Ngultrum).

7. Product Sample

a. One unit pack of product sample from an actual production batch must be submitted at the time of application for registration
b. The product sample may vary depending on the type of packaging used as follows:
    i. Tablet: 10 numbers
    ii. Capsule: 10 numbers
    iii. Pellet: 10 numbers
    iv. Suppository and Pessary: 10 numbers
    v. Semi-solid preparations (creams, ointments, gels, pastes, etc...): 1 unit pack
    vi. IV fluid: 1 unit pack
    vii. Powder: 1 unit pack
    viii. Solution: 1 unit pack
    ix. Spray: 1 unit pack
c. For the purpose of testing, additional sample should be submitted by the MAH at free of cost as per the sample

size determined by the testing laboratory and/or as per sampling guideline of the Authority

d. Sample must be intact, in final commercial pack along with product insert/patient information leaflet (where applicable)
e. Sample must have a remaining shelf-life of at least 50% of the claimed shelf-life at the time of submission
f. Controlled drugs or medicines requiring cold chain monitoring may be exempted from submission of sample.

8. Specimen of Package, Label and Insert

a. Specimen of the original package including primary label, secondary label and product insert/patient information leaflet (where applicable) should be submitted
b. The specifications of products available in the market must be the same as the specimen submitted at the time of application for registration
c. The product label should contain the following information:
   i. Product name
   ii. Dosage form
   iii. Name and strength of active ingredient(s)/ content of formulation with quantity of ingredients per dosage unit,
   iv. Batch no.
   v. Date of manufacture
   vi. Date of expiry
   vii. Pharmacopoeia/compendia standard where applicable
   viii. Route of administration (where applicable)
   ix. Storage conditions
   x. Name and address of the manufacture
   xi. Pack size (unit/volume)
   xii. Warnings/ cautions/precautionary information (where applicable)
   xiii. Directions for handling, where applicable

xiv. Withdrawal Period (applicable to product by food producing animals)
xv. The words “For animal use only” or words bearing similar meaning
xvi. If the product is without an outer carton, the inner label should bear all the information that is required
xvii. The specimen of the original package including primary label, secondary label and product insert/Patient information leaflet must be made from good quality material

d. **A product insert should contain the following information where applicable:**
   i. Product Name
   ii. Name and strength of active ingredient (s)
   iii. Product description
   iv. Pharmacodynamics / Pharmacokinetic
   v. Indication
   vi. Recommended dose
   vii. Mode of administration
   viii. Contraindication
   ix. Warnings and precautions
   x. Drug interactions
   xi. Pregnancy and lactation
   xii. Undesirable effects
   xiii. Overdose and treatment
   xiv. Withdrawal period
   xv. Storage condition
   xvi. Dosage forms and packaging available

Product Information

The product information should contain the following information on drug product:

a) Generic or International Nonproprietary name (INN)
b) Brand name or trade name (if applicable)
c) Dosage form

d) Strength
e) Pharmacopoeia/compendia or In-house specifications;
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
h) Commercial presentation of packaging and pack size
i) The therapeutic category/pharmacological classification to which the pharmaceutical product belongs
j) Target species
k) Dose and directions for use for each indication
l) Mechanism of Action(s) for the claimed indication;
m) List of all the major and common side effects. Side effects specific to the particular drug including newly recognized side effects should be identified
n) Information on use in pregnancy, breastfeeding and other special group of patients including known contraindications and compatibility of use of the finished product during pregnancy and breastfeeding
o) For food producing animals, withdrawal period and Maximum Residual Limit should be submitted.

PART II: QUALITY DATA

1. **Quality Overall Summary:** As per annexure 5

2. Drug Substance and Excipient

a. International non–proprietary name (INN), compendial name if relevant, Laboratory code (if applicable) or chemical name of drug substance and excipients.
b. Physicochemical properties of the drug substance
c. Technical or quality specification of drug substance and excipients.
d. Compendial reference of drug substance and excipients.
e. Certificate of analysis of drug substance and excipients.
f. Details of the manufacturer of drug substances.

3. Drug Product

a. description of the drug product and its composition.
b. copy of monograph for drug product from official compendia should be submitted for compendial drug products.
c. copy of an official compendia monograph and test methods referenced for the in-house method if the product is tested on the basis of a monograph in official compendia and in-house methods.
d. detailed method of analysis including validation process and reports for drug product manufactured using in-house specifications.

4. Manufacturing Process

a. Flow diagram giving the steps of the process and showing where materials enter the process. The critical steps and process controls, intermediate tests or final product controls are conducted should be identified.
b. 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 greater detail.
c. list of equipment used during the manufacture
d. Appropriate process parameters should be identified, such as time, temperature, or pH in each critical step of the process.
e. 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.

f. detailed aseptic requirements for production of sterile products. This shall include data on how sterilization is carried out and controlled.
g. control of critical steps and intermediates in manufacture (IPQC).
h. process validation for drug products manufactured using in-house specifications.
i. analytical procedure used for testing the drug product manufactured using in-house specifications.
j. validation of analytical procedures used for testing the drug product manufactured using in-house specifications.

5. Certificate of Analysis of Drug Product

All the test parameters specified under compendial monograph and in-house method should be performed where applicable.

6. Container Closure System

a. Description of container closure system including the identity of materials of construction of each primary packaging and secondary package with their specifications.
b. Certificate of analysis of package, label and inserts (where applicable).
c. The suitability of the container closure system used shall be as per WHO Annex 9, WHO Technical report series, No. 902, 2002 and its subsequent versions.

7. Product Stability

a. Stability study protocol should at least contain the following:
    i. number of batches and different batch sizes, if applicable

ii. relevant physical, chemical, microbiological and biological test parameters with acceptance criteria
iii. description of the container-closure system
iv. testing frequency
v. description of the conditions of storage (standardized conditions for long-term testing and accelerated)

b. Stability study should be continued for the full period to validate the predicted shelf life.
c. Where not available, the real time stability data at the time of submission should be at least six months for GDA and 12 months for NDA. It should be submitted with letter of commitment for submission of report after the completion of the study.
d. For accelerated stability study , a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months) from a six month study is recommended.
e. Reports for both accelerated stability study and real time stability study should be submitted as per the storage conditions specified in *table 1*.
f. The detail guideline on conducting stability study can be referred from Annexure 10, WHO Technical Report Series, No.1010, 2018 or its subsequent versions.

Type of containers/ packaging in which medicinal products are packed	**Storage Conditions**	
	Long term	**Accelerated**
General Case and impermeable containers	30°C ± 2°C/75% RH ± 5% RH	40°C ± 2°C/75% RH ± 5% RH
Semi permeable containers	30°C ± 2°C/35% RH ± 5% RH	40°C ± 2°C/not more than (NMT) 25 % RH ± 5% RH

Storage in a refrigerator	5°C ± 3°C	25°C ± 2°C/60% RH ± 5% RH
Storage in a freezer	-20°C ± 5°C	-
Storage below -20°C	Case-by-case basis	Case-by-case basis

Table 1 Storage Conditions for Stability Study.

PART III: NON-CLINICAL DOCUMENT

1. Non-clinical document is not required for Generic Products (GDA).

2. For NDA, following documents should be submitted:
   a. Environmental safety
   b. Metabolism and residue kinetics
   c. Toxicology
   d. Target animal safety and
   e. Antimicrobial safety for antimicrobial veterinary medicinal products.

3. For detailed requirement on non-clinical documents, refer VICH Guidelines or any other guidelines recognized by the Authority for this purpose

PART IV: CLINICAL DOCUMENT

1. Clinical document is not required for Generic Products (GDA)

2. For NDA, following documents should be submitted:
   a. Good Clinical Practice
   b. Bioequivalence
   c. Efficacy of anthelmintic for anthelmintic drugs

3. For detailed requirement on clinical documents, refer VICH Guidelines or any other guidelines recognized by the Authority for this purpose.

SECTION C: TRADITIONAL MEDICINES (SOWARIGPA)

PART I: ADMINISTRATIVE DATA AND PRODUCT INFORMATION

Administrative Data

1. Site Master File as per the WHO/PICS format

2. Current Good Manufacturing Practices (cGMP) certificate

cGMP certificate should:

a. bear the name and address of the manufacturer, the date of certification and identity of the issuing authority
b. be valid and should have remaining validity of at least three months during the time of submission; otherwise an 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

Contract manufacturing license status where applicable must be reflected and technical agreement or certificates should be submitted.

Manufacturing license should:

a. bear the name and address of the manufacturer, the date of certification and identity of the issuing authority
b. be valid and should have remaining validity of at least three months during the time of submission; otherwise an evidence of application or under process letter for renewal of same issued by the licensing authority must be submitted along with the license
c. contain the list of products applied for registration

4. Certificate of the Pharmaceutical Product (CoPP)

The CoPP issued solely for export purpose will not be accepted.

CoPP should:

a. bear the date of issue, the name of the product, manufacturer and details of the issuing authority
b. should have remaining validity of at least three months during the time of submission; otherwise an evidence of application or under process letter for renewal of same issued by the licensing authority must be submitted along with the certificate

c. originate from the country where the product is being manufactured
d. reflect/specify Bhutan as the importing country
e. contain the information as per WHO format

5. Letter of Authorization

a. The letter of authorization from the manufacturer should be submitted in the specified format as per annexure 3
b. The regional offices of the principal manufacturer may provide letter of authorization. In such cases, the letter of authorization from the principal manufacturer to these offices must be submitted
c. In case of more than one letter of authorization for the same product, the letter of authorization from the principal company shall be considered
d. In case of more than one letter of authorization from equivalent offices of same manufacturer for the same product(s), the initial one shall be considered.

6. Regulatory Status in other countries

Information regarding countries where the drug product is marketed, approved, withdrawn, if any with reasons, restrictions on use, if any.

7. Price

The price should:
a. indicate MRP
b. be indicated either in USD, INR or local Bhutanese currency (Ngultrum).

8. Product Sample

a. One unit pack of product sample from an actual production batch must be submitted at the time of application for registration;
b. The product sample may vary depending on the type of packaging used as follows:
    i. Tablet: 10 numbers
    ii. Capsule: 10 numbers
    iii. Pellet: 10 numbers

iv. Suppository and Pessary: 10 numbers
v. Semi-solid preparations (creams, ointments, gels, pastes, etc...) : 1 unit pack
vi. IV fluid: 1 unit pack
vii. Powder: 1 unit pack
viii. Solution: 1 unit pack
ix. Spray: 1 unit pack

c. For the purpose of testing, additional sample should be submitted by the MAH at free of cost as per the sample size determined by the testing laboratory and/or sampling guideline of the Authority.
d. Sample must be intact, in final commercial pack along with product insert/patient information leaflet (where applicable);
e. Samples must have a remaining shelf-life of at least 50% of the claimed shelf-life at the time of submission;
f. Controlled drugs or medicines requiring cold chain monitoring may be exempted from submission of sample.

9. Specimen of Package, Label and Insert

a. Specimen of the original package including primary label, secondary label and product insert/patient information leaflet (where applicable) should be submitted;
b. The specifications of products available in the market must be the same as the specimen submitted at the time of application for registration.
c. The product label should contain the following information:
i. Product name
ii. Dosage form
iii. Name and strength of active ingredient(s)/ content of formulation with quantity of ingredients per dosage unit
iv. Batch no.
v. Date of manufacture
vi. Date of expiry
vii. Compendial standard where applicable
viii. Route of administration (where applicable)
ix. Storage conditions

x. Name and address of the manufacture
xi. Pack size (unit/volume)
xii. Warnings/ cautions/precautionary information (where applicable)
xiii. Directions for handling, where applicable
xiv. If the product is without an outer carton, the inner label should bear all the information that is required

d. The specimen of the original package including primary label, secondary label and product insert/Patient information leaflet must be made from good quality material.

e. If the container label is too small for example label of small volume parenterals, not all the above requirements are applicable. At least the following information must be reflected on such labels:
i. Product name
ii. Name and strength of active ingredient(s)
iii. Lot/batch number
iv. Name of the manufacturer, packer, or distributor
v. Date of expiry

f. A product insert should contain the following information where applicable:
i. Product Name
ii. Name and strength of active ingredient (s)
iii. Product description
iv. Pharmacodynamics / Pharmacokinetic
v. Indication
vi. Recommended dose
vii. Mode of administration
viii. Contraindication
ix. Warnings and precautions
x. Drug interactions
xi. Pregnancy and lactation
xii. Undesirable effects
xiii. Overdose and treatment
xiv. Storage condition
xv. Dosage forms and packaging available

Product Information

The product information should contain the following information on drug product;

a. Generic or International Nonproprietary name (INN)
b. Brand name or trade name (if applicable)
c. Dosage form
d. Strength
e. Compendial/ In-house specifications
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
h. Commercial presentation of packaging and pack size
i. The therapeutic category/pharmacological classification to which the pharmaceutical product belongs
j. Dose and directions for use for each indication
k. Mechanism of Action(s) for the claimed indication
l. List of all the major and common side effects. Side effects specific to the particular drug including newly recognized side effects should be identified
m. Information on use in pregnancy, breastfeeding and other special group of patients including known contraindications and compatibility of use of the finished product during pregnancy and breastfeeding

PART II: QUALITY DATA

1. **Quality Overall Summary:** As per annexure 5

2. **Drug Substance and Excipients**

i. International non–proprietary name (INN), Compendial name if relevant, or chemical name(s) of drug substance and excipients.
ii. Physicochemical and other relevant properties of the drug substance.
iii. Technical or quality specification of drug substance and excipients.
iv. Compendial reference of drug substance and excipients.
v. Certificate of analysis of drug substance and excipients.
vi. Name and full addresses including the city and country of the manufacturer of active ingredient.
vii. The drug product should not contain the drug substances included in the Negative List of Substances for Traditional Medicines as per ASEAN.

3. **Certificate of Analysis of Drug Substance**

The Certificate of Analysis of Drug Product should at least contain the following test:

a. Appearance;
b. Identification;
c. Loss on drying or moisture content;
d. Solubility;
e. Microbial contamination test which includes Total Aerobic Microbial Count (TAMC), Total Yeast and Mould Count (TYMC), bile tolerant gram negative bacteria, salmonella, E.coli, staphylococcus aureus, pseudomonas aeruginosa;
f. Heavy metals which includes arsenic, mercury, lead and cadmium;
g. Standardization of extract (assay);
h. Test for Transmissible Spongiform Encephalopathy (TSE)
i. Other test where applicable

4. Drug Product

a. Specifications of the Drug Product

i. A description of the Drug Product and its composition.

ii. A copy of a monograph for drug product from official compendia must be submitted for compendial drug Products.

iii. A copy of an official compendia monograph and test methods referenced for the in-house method if the product is tested on the basis of a monograph in official compendia and in-house methods.

iv. Detailed method of analysis including validation process and reports for Drug Product manufactured using in-house specifications.

b. Certificate of Analysis of Drug Product

The Certificate of Analysis of Drug Product should at least contain the following test:

i. Appearance;

ii. Loss on drying or moisture content;

iii. Solubility;

iv. Microbial contamination test which includes Total Aerobic Microbial Count (TAMC), Total Yeast and Mould Count (TYMC), bile tolerant gram negative bacteria, salmonella, E.coli, staphylococcus aureus, pseudomonas aeruginosa;

v. Heavy metals which includes arsenic, mercury, lead and cadmium;

vi. Uniformity of weight;

vii. Disintegration.

5. Manufacturing Process

a. Flow diagram giving the steps of the process and showing where materials enter the process. The critical steps and process controls, intermediate tests or final product controls are conducted should be identified.

b. A 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 greater detail.

c. List of equipment used during the manufacture
d. Appropriate process parameters should be identified, such as time, temperature, or pH in each critical step of the process.
e. 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.
f. Detailed aseptic requirements for production of sterile products. This shall include data on how sterilization is carried out and controlled.
g. Control of critical steps and intermediates in manufacture (IPQC).
h. Analytical procedure used for testing the drug product manufactured using in-house specifications.
i. Validation of analytical procedures used for testing the drug product manufactured using in-house specification.

6. Product Stability

i. Stability study protocol with following details:
   a) number of batch(es) and different batch sizes, if applicable;
   b) relevant physical, chemical, microbiological and biological test parameters with acceptance criteria or reference to the attached specifications;
   c) description of the container-closure system(s);
   d) testing frequency;
   e) description of the conditions of storage (standardized conditions for long-term testing and accelerated.

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

iii. Stability study should be continued for the full period to validate the predicted shelf life.

iv. Where not available, minimum time period covered by data at submission should be six months for Real time Stability Study for GDA and 12 months for NDA with a letter of commitment for submission of report after the completion of the study

v. At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six month study is recommended.

vi. Reports for both Accelerated Stability Study and Real Time Stability Studies should be submitted as per the storage conditions specified below:

Type of containers/ packaging in which medicinal products are packed	**Storage Conditions**	
	Long term	**Accelerated**
General Case and impermeable containers	30°C ± 2°C/75% RH ± 5% RH	40°C ± 2°C/75% RH ± 5% RH
Semi permeable	30°C ±	40°C ± 2°C/not

containers	2°C/35% RH ± 5% RH	more than (NMT) 25 % RH ± 5% RH
Storage in a refrigerator	5°C ± 3°C	25°C ± 2°C/60% RH ± 5% RH
Storage in a freezer	-20°C ± 5°C	-
Storage below -20°C	case-by-case basis	case-by-case basis

Table 1 Storage Conditions for Stability Study.

The detail guideline on conducting stability study shall be as per Annexure 10, WHO Technical Report Series, No.1010, 2018 and its subsequent updated versions.

SECTION D: HERBAL MEDICINES

PART I: ADMINISTRATIVE DATA AND PRODUCT INFORMATION

Administrative Data

1. **Site Master File as per the WHO/PICS format as annexed**

2. **Current Good Manufacturing Practices (cGMP) certificate**

cGMP certificate should:

a. bear the name and address of the manufacturer, the date of certification and identity of the issuing authority;

b. be valid and should have remaining validity of at least three months during the time of submission; otherwise an 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**

Contract manufacturing license status where applicable must be reflected and technical agreement or certificates should be submitted.

Manufacturing license should:

a. bear the name and address of the manufacturer, the date of certification and identity of the issuing authority

b. be valid and should have remaining validity of at least three months during the time of submission; otherwise an evidence of application or under process letter for renewal of same issued by the licensing authority must be submitted along with the license

c. contain the list of products applied for registration

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

The CoPP issued solely for export purpose will not be accepted**;**

CoPP should:

a. bear the date of issue, the name of the product, manufacturer and details of the issuing authority

b. have remaining validity of at least three months during the time of submission; otherwise an evidence of application or under process letter for renewal of same issued by the licensing authority must be submitted along with the certificate
c. originate from the country where the product is being manufactured
d. reflect/specify Bhutan as the importing country
e. contain the information as per WHO format

5. Letter of Authorization

a. The letter of authorization from the manufacturer should be submitted in the specified format as per annexure 3.
b. The regional offices of the principal manufacturer may provide letter of authorization. In such cases, the letter of authorization from the principal manufacturer to these offices must be submitted
c. In case of more than one letter of authorization for the same product, the letter of authorization from the principal company shall be considered
d. In case of more than one letter of authorization from equivalent offices of same manufacturer for the same product(s), the initial one shall be considered.

6. Regulatory Status in other countries

Information regarding countries where the drug product is marketed, approved, withdrawn, if any with reasons, restrictions on use, if any.

7. Price

The price should:

a) indicate unit MRP
b) be indicated either in USD, INR or local Bhutanese currency (Ngultrum).

8. Product Sample

e. One unit pack of product sample from an actual production batch must be submitted at the time of application for registration

f. The product sample may vary depending on the type of packaging used as follows:
    i. Tablet: 10 numbers
    ii. Capsule: 10 numbers
    iii. Pellet: 10 numbers
    iv. Suppository and Pessary: 10 numbers
    v. Semi-solid preparations (creams, ointments, gels, pastes, etc...) : 1 unit pack
    vi. IV fluid: 1 unit pack
    vii. Powder: 1 unit pack
    viii. Solution: 1 unit pack
    ix. Spray: 1 unit pack

g. For the purpose of testing, additional sample should be submitted by the MAH at free of cost as per the sample size determined by the testing laboratory and/or sampling guideline of the Authority.
h. Sample must be intact, in final commercial pack along with product insert/patient information leaflet (where applicable);
i. Samples must have a remaining shelf-life of at least 50% of the claimed shelf-life at the time of submission;
j. Controlled drugs or medicines requiring cold chain monitoring may be exempted from submission of sample.

9. Specimen of Package, Label and Insert

a. Specimen of the original package including primary label, secondary label and product insert/patient information leaflet (where applicable) should be submitted;
b. The specifications of products available in the market must be the same as the specimen submitted at the time of application for registration.
c. The product label should contain the following information:
    i. Product name
    ii. Dosage form
    iii. Name and strength of active ingredient(s)/ content of formulation with quantity of ingredients per dosage unit
    iv. Batch no.
    v. Date of manufacture

vi. Date of expiry
vii. Compendial standard where applicable
viii. Route of administration (where applicable)
ix. Storage conditions
x. Name and address of the manufacture
xi. Pack size (unit/volume)
xii. Warnings/ cautions/precautionary information (where applicable)
xiii. Directions for handling, where applicable
xiv. If the product is without an outer carton, the inner label should bear all the information that is required

d. The specimen of the original package including primary label, secondary label and product insert/Patient information leaflet must be made from good quality material.

e. If the container label is too small for example label of small volume parenteral, not all the above requirements are applicable. At least the following information must be reflected on such labels:
   i. Product name
   ii. Name and strength of active ingredient(s)
   iii. Lot/batch number;
   iv. Name of the manufacturer, packer, or distributor
   v. Date of expiry

f. A product insert should contain the following information where applicable:
   i. Product Name
   ii. Name and strength of active ingredient (s)
   iii. Product description
   iv. Pharmacodynamics / Pharmacokinetic
   v. Indication
   vi. Recommended dose
   vii. Mode of administration
   viii. Contraindication
   ix. Warnings and precautions
   x. Drug interactions
   xi. Pregnancy and lactation
   xii. Undesirable effects

xiii. Overdose and treatment
xiv. Storage condition
xv. Dosage forms and packaging available

Product Information

The product information should contain the following information on drug product;

a. Generic or International Nonproprietary name (INN);
b. Brand name or trade name (if applicable);
c. Dosage form;
d. Strength;
e. Compendial/ In-house specifications;
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;
h. Commercial presentation of packaging and pack size;
i. The therapeutic category/pharmacological classification to which the pharmaceutical product belongs;
j. Dose and directions for use for each indication;
k. Mechanism of Action(s) for the claimed indication;
l. List of all the major and common side effects. Side effects specific to the particular drug including newly recognized side effects should be identified;
m. Information on use in pregnancy, breastfeeding and other special group of patients including known contraindications and compatibility of use of the finished product during pregnancy and breastfeeding;

PART II: QUALITY DATA

1. **QOS:** Quality Overall Summary: As per annexure 5

2. **Drug Substance and Excipients**
   a. International non–proprietary name (INN), compendial name if relevant, or chemical name(s) of drug substance and excipients.
   b. Physicochemical and other relevant properties of the drug substance.
   c. Technical or quality specification of drug substance and excipients.
   d. Compendial reference of drug substance and excipients.
   e. Certificate of analysis of drug substance and excipients.
   f. Name and full addresses including the city and country of the manufacturer of active ingredient.
   g. The drug product should not contain the drug substances included in the Negative List of Substances for Traditional Medicines as per ASEAN.

3. Certificate of Analysis of Drug Substance

The Certificate of Analysis of Drug Product should at least contain the following test:

a. Appearance;
b. Identification;
c. Quantitative assay;
d. Loss on drying or moisture content;
e. Solubility;
f. Microbial contamination test which includes Total Aerobic Microbial Count (TAMC), Total Yeast and Mould Count (TYMC), bile tolerant gram negative bacteria, salmonella, E.coli, staphylococcus aureus, pseudomonas aeruginosa;
g. Heavy metals which includes arsenic, mercury, lead and cadmium;
h. Standardization of extract (assay);
i. Test for Transmissible Spongiform Encephalopathy (TSE)
j. Other test where applicable

4. Drug Product

a. A description of the Drug Product and its composition.

b. A copy of a monograph for drug product from official compendia must be submitted for compendial drug Products.

c. A copy of an official compendia monograph and test methods referenced for the in-house method if the product is tested on the basis of a monograph in official compendia and in-house methods.

d. Detailed method of analysis including validation process and reports for Drug Product manufactured using in-house specifications.

5. Certificate of Analysis of Drug Product

The Certificate of Analysis of Drug Product should at least contain the following test:

a. Appearance;
b. Quantitative assay;
c. Loss on drying or moisture content;
d. Solubility;
e. Microbial contamination test which includes Total Aerobic Microbial Count (TAMC), Total Yeast and Mould Count (TYMC), bile tolerant gram negative bacteria, salmonella, E.coli, staphylococcus aureus, pseudomonas aeruginosa;
f. Heavy metals which includes arsenic, mercury, lead and cadmium;
g. Uniformity of weight;
h. Disintegration.

6. Manufacturing Process

a. A flow diagram giving the steps of the process and showing where materials enter the process. The critical steps and process controls, intermediate tests or final product controls are conducted should be identified.
b. A 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 greater detail.

c. List of equipment used during the manufacture
d. Appropriate process parameters should be identified, such as time, temperature, or pH in each critical step of the process.
e. 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.
f. Detailed aseptic requirements for production of sterile products. This shall include data on how sterilization is carried out and controlled.
g. Control of critical steps and intermediates in manufacture (IPQC).
h. Analytical procedure used for testing the drug product manufactured using in-house specifications.
i. Validation of analytical procedures used for testing the drug product manufactured using in-house specifications.

7. Container Closure System

a. Description of container closure system including the identity of materials of construction of each primary packaging and secondary package with their specifications.
b. Certificate of analysis of package, label and inserts (where applicable).
c. The suitability of the container closure system used shall be as per WHO Annex 9, WHO Technical report series , No. 902, 2002 and its subsequent updated versions.

8. Product Stability

a. Stability study protocol with following details:
i. number of batch(es) and different batch sizes, if applicable;
ii. relevant physical, chemical, microbiological and biological test parameters with acceptance criteria or reference to the attached specifications;

iii. description of the container-closure system(s);
iv. testing frequency;
v. description of the conditions of storage (standardized conditions for long-term testing and accelerated.
vi. Results of the stability studies presented in an appropriate format such as tabular, graphical, or narrative.
vii. Stability study should be continued for the full period to validate the predicted shelf life.
viii. Where not available, minimum time period covered by data at submission should be six months for Real time Stability Study for GDA and 12 months for NDA with a letter of commitment for submission of report after the completion of the study.
ix. At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six month study is recommended.
x. Reports for both Accelerated Stability Study and Real Time Stability Studies should be submitted as per the storage conditions

Type of containers/ packaging in which medicinal products are packed	**Storage Conditions**	
	Long term	**Accelerated**
General Case and impermeable containers	30°C ± 2°C/75% RH ± 5% RH	40°C ± 2°C/75% RH ± 5% RH
Semi permeable containers	30°C ± 2°C/35% RH ± 5% RH	40°C ± 2°C/not more than (NMT) 25 % RH ± 5% RH
Storage in a refrigerator	5°C ± 3°C	25°C ± 2°C/60% RH ± 5% RH
Storage in a freezer	-20°C ± 5°C	-

Storage below -20°C		

Table 1 Storage Conditions for Stability Study.

The detail guideline on conducting stability study shall be as per Annexure 10, WHO Technical Report Series, No.1010, 201

PART III: NON-CLINICAL DOCUMENT

1. Non-clinical document is not required for Generic Products (GDA).

2. For NDA, following documents should be submitted:
   a. Pharmacology
   b. Pharmacokinetics
   c. Toxicology

3. For detailed requirement on non-clinical documents, refer ICH CTD Guidelines: M4S (Safety) or ACTD part III: Nonclinical Guidelines or any other guidelines recognized by the Authority for this purpose.

PART IV: CLINICAL DOCUMENT

1. Clinical document is not required for Generic Products (GDA).

2. For NDA, following documents should be submitted:

    a. Biopharmaceutics and associated analytical methods
    b. Clinical Pharmacology Studies
    c. Clinical Efficacy
    d. Clinical Safety

3. For detailed requirement on clinical documents, refer ICH CTD Guidelines: M4E (Efficacy) and E3, or the ACTD part IV: Clinical Guidelines or any other guidelines recognized by the Authority for this purpose.

SECTION E: APIs FOR EXTEMPORANEOUS PREPARATION

PART I: ADMINISTRATIVE DATA AND PRODUCT INFORMATION

Administrative Data

1. **Site Master File as per the WHO/PICS format as annexed**

2. **Current Good Manufacturing Practices (cGMP) certificate**

   cGMP certificate should:

   a. bear the name and address of the manufacturer, the date of certification and identity of the issuing authority
   b. be valid and should have remaining validity of at least three months during the time of submission; otherwise an 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:

   a. bear the name and address of the manufacturer, the date of certification and identity of the issuing authority
   b. be valid and should have remaining validity of at least three months during the time of submission; otherwise an evidence of application or under process letter for renewal of same issued by the licensing authority must be submitted along with the license
   c. contain the list of products applied for registration
   d. contract manufacturing license status where applicable must be reflected and technical agreement or certificates should be submitted.

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

   The CoPP issued solely for export purpose will not be accepted**;**

   CoPP should:

a. bear the date of issue, the name of the product, manufacturer and details of the issuing authority
b. have remaining validity of at least three months during the time of submission; otherwise an evidence of application or under process letter for renewal of same issued by the licensing authority must be submitted along with the certificate.
c. originate from the country where the product is being manufactured
d. reflect/specify Bhutan as the importing country
e. contain the information as per WHO format

5. Letter of Authorization

a. The letter of authorization from the manufacturer should be submitted in the specified format as per annexure 3
b. The regional offices of the principal manufacturer may provide letter of authorization. In such cases, the letter of authorization from the principal manufacturer to these offices must be submitted;
c. In case of more than one letter of authorization for the same product, the letter of authorization from the principal company shall be considered;
d. In case of more than one letter of authorization from equivalent offices of same manufacturer for the same product(s), the initial one shall be considered.

6. Regulatory Status in other countries

Information regarding countries where the drug product is marketed, approved, withdrawn, if any with reasons, restrictions on use, if any.

7. Price

The price should:

a. indicate unit MRP
b. be indicated either in USD, INR or local Bhutanese currency (Ngultrum).

8. Product Sample

a. One unit pack of product sample from an actual production batch must be submitted at the time of application for registration
b. The product sample may vary depending on the type of packaging used as follows:
    i. Semi-solid preparations(creams, ointments, gels, pastes, etc...) : 1 unit pack
    ii. Powder: 1 unit pack
    iii. Solution: 1 unit pack

c. For the purpose of testing, additional sample should be submitted by the MAH at free of cost as per the sample size determined by the testing laboratory and/or sampling guideline of the Authority.

d. Samples must be intact, in final commercial pack along with product insert/patient information leaflet (where applicable);
e. Samples must have a remaining shelf-life of at least 50% of the claimed shelf-life at the time of submission
f. Controlled drugs or medicines requiring cold chain monitoring may be exempted from submission of sample

9. Specimen of Package, Label and Insert

a. Specimen of the original package including primary label, secondary label and product insert/patient information leaflet (where applicable) should be submitted
b. The specifications of products available in the market must be the same as the specimen submitted at the time of application for registration.
c. The product label should contain the following information:
    i. Product name
    ii. Dosage form

iii. Name and strength of active ingredient(s)/ content of formulation with quantity of ingredients per dosage unit,
iv. Batch no.
v. Date of manufacture
vi. Date of expiry
vii. Compendial standard where applicable
viii. Route of administration (where applicable)
ix. Storage conditions
x. Name and address of the manufacture
xi. Pack size (unit/volume)Warnings/ cautions/precautionary information (where applicable)
xii. 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 specimen of the original package including primary label, secondary label and product insert/Patient information leaflet must be made from good quality material.
f. If the container label is too small for example label of small volume parenterals, not all the above requirements are applicable. The following information must be reflected on such labels:
Product name
i. Name and strength of active ingredient(s)
ii. Lot/batch number;
iii. Name of the manufacturer, packer, or distributor
iv. Date of expiry
g. A product insert should contain the following information where applicable:
i. Product Name
ii. Name and strength of active ingredient (s)
iii. Product description
iv. Pharmacodynamic/Pharmacokinetic
v. Indication

vi. Recommended dose
vii. Mode of administration
viii. Contraindication
ix. Warnings and precautions
x. Drug interactions
xi. Pregnancy and lactation
xii. Undesirable effects
xiii. Overdose and treatment
xiv. Storage condition
xv. Dosage forms and packaging available

Product Information

The product information should contain the following information on drug product;

a. Generic or International Nonproprietary name (INN)
b. Brand name or trade name (if applicable)
c. Dosage form
d. Strength
e. Compendial/ In-house specifications
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
h. Commercial presentation of packaging and pack size
i. The therapeutic category/pharmacological classification to which the pharmaceutical product belongs
j. Dose and directions for use for each indication
k. Mechanism of Action(s) for the claimed indication
l. List of all the major and common side effects. Side effects specific to the particular drug including newly recognized side effects should be identified
m. Information on use in pregnancy, breastfeeding and other special group of patients including known contraindications and compatibility of use of the finished product during pregnancy and breastfeeding

Part III- Quality Profile

1**. Manufacturing/Repacking process**

Manufacturing process of the product should include following:

a. Procedures and records to indicate that controls are in place to avoid mix-up, contamination and cross contamination.

b. Method to detect the impurities

c. List of solvents or other raw materials used for manufacture or repacking.

2. **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:

a. Contain the result of all critical parameters as specified in the Pharmacoepias

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

c. Be dated with the date of analyses and signed by a authorized person against the name.

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

e. 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.

PART III: NON-CLINICAL DOCUMENT

1. Non-clinical document is not required for Generic Products (GDA).

2. For NDA, following documents should be submitted:
    a. Pharmacology
    b. Pharmacokinetics
    c. Toxicology

3. For detailed requirement on clinical document, refer ICH CTD Guidelines: M4S (Safety) or ACTD part III: Nonclinical Guidelines or any other guidelines recognized by the Authority.

PART IV: CLINICAL DOCUMENT

1. Clinical document is not required for generic product (GDA).

2. For NDA, following documents should be submitted:
    a. Biopharmaceutics and associated analytical methods
    b. Clinical Pharmacology Studies
    c. Clinical Efficacy
    d. Clinical Safety

3. For detailed requirement on clinical document, refer ICH CTD Guidelines: M4E (Efficacy) and E3, or ACTD part IV: Clinical Guidelines or any other guideline recognized by the Authority for this purpose.

Annexures

Annexure 1: Application forms

APPLICATION FOR FULL REGISTRATION OF MEDICINES

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

Type of medicines (*Circle the appropriate one*):

i. Human Allopathic
ii. Veterinary Allopathic
iii. Sowa-Rigpa
iv. Herbal
v.API for extemporaneous preparation

Product	Pack	Composition (With Strength)	Manufacturer

Declaration (please tick the boxes):

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

☐ I declare that I have read the regulation and I am fully aware that my application may be rejected if I do not fulfill the conditions or contravenes the provision(s) of the act and regulations made there under.

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

Dated Signature of applicant
with name and contact No.

APPLICATION FOR ABRIDGE REGISTRATION OF MEDICINES

M/s……....hereby apply for abridged registration of the product specified below for sale/distribution in Bhutan.

The product has been approved by one of the PIC/S member countries or WHO or by International agencies.

Name of the country(s)/agency(s):.....

Product	Pack	Composition (With Strength)	Manufacturer

Declaration (please tick the boxes):

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

☐ I declare that I have read the regulation and I am fully aware that my application may be rejected if I do not fulfill the conditions or contravenes the provision(s) of the act and regulations made there under.

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

Dated Signature of applicant
with name and contact No.

APPLICATION FORM FOR EXPEDITED REGISTRATION OF MEDICINES

M/s…….....hereby apply for expedited registration of the product specified below for sale/distribution in Bhutan as per the Product Registration Guideline.

Product	Pack	Composition (With Strength)	Manufacturer

I hereby declare that following conditions are fulfilled (please tick the boxes):

☐ Minimum of 5 products with valid registration status registered with DRA for minimum of 2 years at the time of application;

☐ No past record of product recall or withdrawal from Bhutan (voluntarily recalls by Manufacturers do not apply);

☐ Not more than 2 post registration change applied for a single product in one year;

☐ For parenteral, at least one parenteral product to be registered amongst the 5 valid.

OR

☐ cGMP compliant manufacturer verified from the GMP inspection report of the Authority and/or other MRA wherever applicable;

OR

☐ Registered by at least two other MRAs.

Declaration (please tick the boxes):

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

☐ I declare that I have read the regulation and I am fully aware that my application may be rejected if I do not fulfill the conditions or contravenes the provision(s) of the act and regulations made there under.

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

Dated Signature of applicant
with name and contact No.

APPLICATION FOR RENEWAL OF REGISTRATION OF MEDICINES

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

Product Registration no:
Name of the product:
Date of Expiry of the Registration:

Product	Pack	Composition (With Strength)	Manufacturer

Declaration (please tick the boxes):

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

☐ I declare that I have read the regulation and I am fully aware that my application may be rejected if I do not fulfill the conditions or contravenes the provision(s) of the act and regulations made there under.

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

Dated Signature of applicant
with name and contact No.

APPLICATION FOR POST APPROVAL VARIATIONS OF MEDICINES

M/s……hereby apply for post approval changes of the following product:

Product Registration Number:

Name of the Product:

Proposed Variations (*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*)

Declaration (please tick the boxes):

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

☐ I declare that I have read the regulation and I am fully aware that my application may be rejected if I do not fulfill the conditions or contravenes the provision(s) of the act and regulations made there under.

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

Dated Signature of applicant
with name and contact No

Annexure 2: List of requirements for registration of an FDC in each type of FDC

Requirement	Type 1 FDC	Type 2 FDC	Type 3 FDC	Type 4 FDC
Rationale for combination	NA	NA	Required	Required
Balancing advantages & disadvantages of the combination	NA	NA	Required	Required
Marketing status in other countries	Required	Required	Required	Required
Analysis of literature data	NA	NA	Required	Required
Pharmaceutical development studies	Required	Required	Required	Required
A full quality data set	Required	Required	Required	Required
Bioavailability data	NA	NA	Consider case by case	Consider case by case
Bioequivalence date	NA	NA	Consider case by case	Consider case by case
Preclinical Pharmacology and safety	NA	NA	Consider case by case	Consider case by case
Clinical safety and	NA	NA	Consider	Consider

efficacy			case by case	case by case
Product information	Required	Required	Required	Required
Periodic PSUR submission	Required	Required	Required	Required
Risk benefit analysis	Required	Required	Required	Required

Annexure 3: Format for Letter of Authorization

Letter head of the Company

Date:……

Letter of Authorization

M/s ***(name of the firm)***……having our registered office at ***(address of the firm including name of place, country)***……. hereby authorize ***(name of the authorization holder including government ministry, procurement agency, Market Authorization Holder)***……having its office in Bhutan to apply and obtain registration certificate of the following medicinal products from Drug Regulatory Authority of Bhutan.

1. (name of product)

2.(name of product)

(Name of authorization holder)…….. shall be sole dealer responsible for above product/s from the company and will be accountable for the performance of above products in Bhutan.

Further, the invoice will be generated from the (***name of the firm or regional office etc of the company)***…… which will be used for applying for Import Authorization.

This letter of Authorization shall be valid for a period of (number of years)…….. from above date unless suspended or revoked, the reason of which will be shared with Drug Regulatory Authority, Bhutan,

This authorization cannot be assigned, transferred and/or sub delegated to any person or party without written approval from principle manufacturer.

Authorized signatory
(Managing Director)
Name of the firm

(seal and logo)

Annexure 4: Data requirement for Post Approval Variation

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

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

	except for the intended change. 4. Relevant document/reference to support the changes (where applicable). 5. Product Sample with proposed change, the quantity as defined above under data requirements.

Type of post approval variation: 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 B for at least 3 different batches. Both real time and accelerated stability test report must be submitted 4. Information and data on package and label. 5. Letter of declaration from the manufacturer and MAH stating that no other changes on the label except for the intended change. 6. Price structure for the new pack. 7. Certificate of analysis for the finished product. 8. Product Sample with proposed change.

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

Type of post approval variation: price structure	
Conditions to be fulfilled	There is no change to the product except for the intended change
Documents to be submitted	1. Price Structure of the product.

Type of post approval variation: Change in any part of the (primary) packaging material not in contact with the finished product formulation such as colour of flipoff caps, colour code rings on ampoules	
Conditions to be fulfilled	The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product
Documents to be submitted	1. Information and data on package and label 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Letter of declaration from the manufacturer and MAH stating that no other changes except for the intended change. 4. Price Structure, if changed. 5. Product sample with proposed change.

Type of post approval variation: Reduction/Increase in shelf-life of the finished product. **a) As a package for sale and/or** **b) After first opening and/or** **c) After dilution/reconstitution**	
Conditions to be fulfilled	1. For (a) & (b) - The studies must show conformance to the currently approved shelf- life specification. 2. For (c) – The studies must show conformance to the currently approved shelf life specification for the reconstituted product.
Documents to be submitted	1. Results of appropriate real time stability studies covering the duration of proposed shelf-life of at least two pilot/production scale batches of the product in the authorized packaging material. 2. Revised drafts of the package insert and labeling

	incorporating the proposed variation (where applicable). 3. Justification letter for the change of shelf- life of the finished product (where applicable). 4. Letter of declaration from the manufacturer and MAH stating that no other changes on the label except for the intended change.

Type of post approval variation: Change of the name or address (for example: postal code, street name) of the manufacturer of finished product	
Conditions to be Fulfilled	1. The manufacturing site remains the same. 2. Not applicable to the case in which it involves change in ownership of the manufacturer. 3. No other changes except for the change of the name and/or address of a manufacturer of the finished product.
Documents to be submitted	1. Official letter from the manufacturer requesting for the change in name/address of the plant. 2. A valid GMP certificate, CoPP which covers the GMP certification or official document from relevant authority confirming the new name and/or address. 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 on the label except for the intended change. 4. Product sample 5. Price Structure, if applicable

Type of post approval variation: Change in storage conditions	
Conditions to be fulfilled	There is no change to the product except for the intended change
Documents to be submitted	1. Stability test report 2. Letter of declaration from the manufacturer and MAH stating that no other changes on the label except for the intended change. 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 4. Product Sample with proposed change.

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

Type of post approval variation: 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, contraindication or adverse events/effects to the approved product labels

Documents to be submitted	1. Official letter stating: (a) the reasons for the notification, *AND*, (b) the status of the proposed changes in other countries. 2. Letter of declaration from the manufacturer and MAH stating that no other changes on the label except for the intended change and that the changes are supported by data 3. Product Sample with proposed change.

Type of post approval variation: Change of Compendial 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 compendia 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 compendial Standard. 3. Revised draft package, insert and labeling incorporating the proposed change. 4. Updated Certificate of Pharmaceutical Product (CoPP) (where applicable). 5. Price structure, if applicable 6. Product Sample
Type of post approval variation: Substitution of the raw materials in case of Sowarigpa medicines	
Conditions to be fulfilled	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
Documents to be submitted	1. Justification for change 2. Official letter from manufacturer authorizing the

	substitution 3. A declaration letter from the manufacturer and MAH that there is no other changes to the product/label except for the intended change 4. Revised draft package, insert and labeling incorporating the proposed change. 5. Photocopies of gso-ba-rig-pa text references which have such similar therapeutic indications 6. Price structure, if applicable 7. Product Sample

Type of post approval variation: Substitution of the specifications for the pre-processed raw materials in case of gSo-Ba-arig-pa medicines	
Conditions to be fulfilled	There is no change to the product (formulation, release and shelf-life specifications, manufacturing source and process) except for the specifications of the pre-processed raw materials
Documents to be submitted	1. Justification for change 2. A declaration letter from the manufacturer and MAH that there is no other changes to the product/label except for the intended change. 3. Test Report on pre-processed raw materials 4. A copy of preprocessing method from *g.so-rig-pa* text if available or a copy of method used. 5. Price structure, if applicable 6. Product Sample with proposed change.

Annexure 5: Quality Overall Summary

No.	Parameters	Components	Requirements	
			GDA	NDA
S	DRUG SUBSTANCE			
S1	General Information 1.1. Nomenclature	1.1.1 Information from the S1	Yes	Yes
	1.2. Structure	1.2.1 Structural formula, including relative and absolute stereochemistry, the molecular	No	Yes
	1.3. General properties	1.3.1 Physico-chemical characteristics and other relevant properties including biological activity for biotech.	Yes	Yes
S2	Manufacture 2.1 Manufacturer(s)	2.1.1 Name and Address of Manufacturer(s)	Yes	Yes
	2.2 Description of Manufacturing Process and Process Controls	2.2.1 The description of the drug substance manufacturing process and process control that represents the applicant's commitment for the manufacture of the drug substances.	No	Yes

		2.2.2	Information on the manufacturing process, which typically starts with a vial(s) of the cell bank, and include cell culture, harvest(s), purification and modification reaction, filling, storage and shipping conditions.	No	No
	2.3 Control of Materials	2.3.1	Starting materials, solvents, reagents, catalysts, and any other materials used in the manufacture of the drugs substance indicating where each material is used in the process. Tests and acceptance criteria of these materials	No	Yes
		2.3.2	Control of source and starting materials of biological origin.	No	No
		2.3.3	Source, history and generation of the cell substrate.	No	No
		2.3.4	Cell banking system, characterization and testing.	No	No
		2.3.5	Viral safety evaluation.	No	No

	2.4 Controls of Critical Steps and Intermediates	2.4.1	Critical steps: Tests and acceptance criteria, with justification including experimental data, performed at critical steps of the manufacturing process to ensure that the process is controlled.	No	Yes
		2.4.2	Intermediates: Specifications and analytical procedure, if any, for intermediates isolated during the process.	No	Yes
		2.4.3	Stability data	No	No
	2.5 Process Validation and/or Evaluation	2.5.1	Process validation and/or evaluation studies for aseptic processing and sterilization.	No	Yes
	2.6 Manufacturing Process Development	2.6.1	Description and discussion of significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing non- clinical, clinical, scale-up, pilot and if available, production scale batches.	No	Yes

		2.6.2	The development history of the manufacturing process as described in S 2.2	No	No
S3	Characterization 3.1 Elucidation of Structure and other characteristics	3.1.1	Confirmation of structure based on e.g. synthetic route and spectral analyses	No	Yes
		3.1.2	Compendial requirements or appropriate information from the manufacturer	No	No
		3.1.3	Details on primary, secondary and higher-order structure and information on biological activity, purity and immunochemical properties (when relevant).	No	No
	3.2. Impurities	3.2.1	Summary of impurities monitored or tested for during and after manufacture of drug substance	No	Yes
		3.2.2	Compendial requirements or appropriate information from the manufacturer	No	No
S4	Control of Drug Substance 4.1. Specification	4.1.1	Detailed specification, tests and acceptance criteria.	No	Yes
		4.1.2	Compendial specification or	No	No

			appropriate information from the manufacturer		
		4.1.3	Specify source, including as appropriate species of animal, type of microorganism, etc.	No	No
	4.2. Analytical Procedures	4.2.1	The analytical procedures used for testing of drug substance.	No	Yes
		4.2.2	Compendial specification or appropriate information from the manufacturer	Yes	No
	4.3 Validation of Analytical Procedures	4.3.1	Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance	No	Yes
		4.3.2	Non-compendial methods	No	No
	4.4. Batch Analyses	4.4.1	Description of batches and results of the analysis to establish the specification.	No	Yes
	4.5. Justification of Specification	4.5.1	Justification for drug substance specification.	No	Yes
S5	5.1 Reference Standards or Materials	5.1.1	Information on the reference standards or reference materials used for testing of the drug substance.	No	Yes

		5.1.2	Compendial reference standard.	Yes	No
S6	6.1 Container Closure System	6.1.1	Descriptions of the container closure systems.	No	Yes
S7	7.1 Stability	7.1.1	Stability report.	No	Yes
		7.1.2	Literature data.	Yes	No
P	**DRUG PRODUCT**				
P1	1.1 Description and Composition	1.1.1	Description	Yes	Yes
		1.1.2	Dosage form and characteristics.	No	No
		1.1.3	Accompanying reconstitution diluent (s) if any.	No	NO
		1.1.4	Type of container and closure used for the dosage form and reconstitution diluent (s), if applicable.	No	No
		1.1.5	Composition (Name, quantity stated in metric weight or measures, function and quality standard reference).	Yes	Yes
P2	Pharmaceutical 2.1 Information on Development Studies	2.1.1	Data on the development studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological	No	Yes

			attributes and usage instruction are appropriate for the purpose specified in the application.		
	2.2. Components of the Drug Product `	2.2.1	Active ingredient: Justification of the compatibility of the active ingredient with excipients listed in P1.	No	Yes
		2.2.1.1	In case of combination products, justification of the compatibility of active ingredients with each other.	No	No
		2.2.1.2	Literature data.	No	No
		2.2.2	Excipients (Justification of the choice of excipients listed in P1, which may influence the drug product performance).	No	Yes
	2.3. Finished Product	2.3.1	Formulation Development: A brief summary describing the development of the finished product, (taking into consideration the proposed route of administration and usage for NCE and Biotech)	No	Yes

		2.3.2	Overages: Justification of any overage in the formulation(s) described in P1.	No	Yes
		2.3.3	Physicochemical and Biological Properties: Parameters relevant to the performance of the finished product e.g. pH, dissolution	Yes	Yes
	2.4 Manufacturing Process Development	2.4.1	Selection and optimization of the manufacturing process	No	Yes
		2.4.2	Differences between the manufacturing processes used to produce pivotal clinical batches and the process described in P.3.2, if applicable	No	Yes
	2.5. Container Closure System	2.5.1	Suitability of the container closure system used for the storage, transportation (shipping) and use of the finished product.	Yes	Yes
	2.6. Microbiological Attributes	2.6.1	Microbiological attributes of the dosage form, where appropriate	Yes	Yes
	2.7. Compatibility	2.6.2	Compatibility of the finished product with reconstitution diluent(s) or dosage devices.	No	Yes

		2.6.3	Literature data	No	No
P3	Manufacture 3.1. Batch Formula	3.1.1	Name and quantities of all ingredients	Yes	Yes
	3.2. Manufacturing Process and Process Control	3.2.1	Description of manufacturing process and process control	Yes	Yes
	3.3. Control of Critical Steps and Intermediates	3.3.1	Tests and acceptance criteria	Yes	Yes
	3.4. Process Validation and/or Evaluation	3.4.1	Description, documentation, and results of the validation and/or evaluation studies for critical steps or critical assays used in the manufacturing process.	Yes(only for in-house)	Yes
P4	Control of excipients 4.1. Specifications	4.1.1	Specifications for excipients:	No	Yes
		4.1.2	Compendial requirements or appropriate information from the manufacturer	Yes	No
	4.2. Analytical Procedures	4.2.1	Analytical procedures used for testing excipients where appropriate.	No	Yes
		4.2.2	Compendial requirements or appropriate information from the manufacturer	Yes	No

	4.3 Excipient of Human or Animal Origin	4.3.1	Information regarding sources and or adventitious	No	Yes
		4.3.2	Compendial requirements or appropriate information from the manufacturer	No	No
	4.4. Novel Excipients	4.4.1	For excipient(s) used for the first time in a finished product or by a new route of administration, full details of manufacture, characterization and controls, with cross reference to supporting safety data (non- clinical or clinical)	No	Yes
P5	Control of Finished Product 5.1. Specification	5.1.1	The specification(s) for the finished product.	Yes	Yes
	5.2. Analytical Procedures	5.2.1	Analytical procedures used for testing the finished product for in house method	Yes	Yes
	5.3. Validation of Analytical Procedures	5.3.1	Information including experimental data, for the analytical procedure used for testing the finished product	No	Yes
		5.3.2	Non-compendial method	Yes	Yes

		5.3.3	Verification of compendial method applicability - precision & accuracy	No	No
	5.4. Batch Analyses	5.4.1	Description and test results of all relevant batches.	No	Yes
	5.5. Characterization of Impurities	5.5.1	Information on the characterization of impurities	No	Yes
		5.5.2	Compendial requirements or appropriate information from the manufacturer	No	No
	5.6. Justification of Specification(s)	5.6.1	Justification of the proposed finished product specification(s).	No	Yes
		5.6.2	Compendial requirements or appropriate information from the manufacturer	No	No
P6	6.1 Reference Standards or Materials	6.1.1	Information on the reference standards or reference materials used for testing of the finished product.	No	Yes
		6.1.2	Compendial requirements or appropriate information from the manufacturer	Yes	No
P7	7.1 Container Closure System	7.1.1	Specification and control of primary and secondary packaging material, type of	Yes	Yes

			packaging and the package size, details of packaging inclusion (e.g. desiccant, etc)		
P8	8.1 Stability	8.1.1	Stability report: data demonstrating that product is stable through its proposed shelf life.	Yes	Yes
		8.1.2	Commitment on post approval stability monitoring	No	No
P9	Product Interchangeability	9.1.1	In Vitro: Comparative dissolution study as Required	Yes	No
	9.1 Equivalence evidence	9.1.2	In Vivo: Bioequivalence study as required	Yes	No

Annexure 6: Format for Declaration Letter

Letter head of the Company

Date:……

Declaration Letter

M/s **(name of the firm)**……having our registered office at **(address of the firm including name of place, country)**……. hereby declare that there is no change in any aspect of the product which is registered with the Drug Regulatory Authority of Bhutan for the purpose of renewal of registration. The aspects shall include but not limited to quality, safety and efficacy of the medicinal product.

The details of the registered medicinal product are as follows:

Product Name:……..
Registration Number:……..
Date of expiry of registration:……

A copy of the medicinal product registration certificate is submitted along with this declaration letter.

Authorized signatory
(Managing Director/Head of the Company)
Name of the firm

(Seal and logo of the company)

Annexure 7: Checklist for Compiling Dossier

Checklist 1: Checklist for preparation of the application for full registration of medicinal products (Part III and IV are not applicable to GDA)

Document	Category of medicines					
	Human Allopathic	Veterinary Allopathic	gSobarigpa	Herbal Medicine	API for Extemporaneous Preparation	Tick if it is available
Application form	Yes	Yes	Yes	Yes	Yes	
Part I: Administrative and Product Profile	Yes	Yes	Yes	Yes	Yes	
Site Master File	Yes	Yes	Yes	Yes	Yes	
Manufacturing License	Yes	Yes	Yes	Yes	Yes	
CoPP	Yes	NA	Yes	Yes	Yes	
Letter of Authorization	Yes	Yes	Yes	Yes	Yes	
Regulatory status in other countries	Yes	Yes	Yes	Yes	Yes	
Price Structure (in Ngultrum, Rupees, US Dollar)	Yes	Yes	Yes	Yes	Yes	
Product Sample	Yes	Yes	Yes	Yes	Yes	
Specimen of Package including primary label,	Yes	Yes	Yes	Yes	Yes	

secondary label and insert						
Product Information	Yes	Yes	Yes	Yes	Yes	
Part II: Quality Data	Yes	Yes	Yes	Yes	Yes	
Quality Overall Summary	Yes	Yes	Yes	Yes	Yes	
Part III: Non Clinical Document (Not applicable to GDA)	Yes	Yes	Yes	Yes	Yes	
Part IV: Clinical Document (Not applicable to GDA)	Yes	Yes	Yes	Yes	Yes	

Name and signature of Competent person

Checklist 2: Checklist for preparation of the application for abridged registration of medicinal products

Documents Required	Tick mark if it is available
Application form	
Documentary evidence to support abridged registration	
Declaration letter	
Letter of Authorization	
Product Sample	
Specimen of Package including primary label, secondary label and insert	
Pack Size of the product	
Price Structure	

Name and signature of authorized person

Checklist 3: Checklist for preparation of the application for expedited registration of medicinal products

Documents Required	Tick mark if it is available
Application form	
Letter of authorization	
Certificate of Analysis of drug product	
Method of analysis of drug product for non-compendia method	
Specimen of Package including primary label, secondary label and insert	
Product Sample	
Price Structure	

Name and signature of authorized person

Checklist 4: Checklist for preparation of the application for renewal registration of medicinal products

Documents Required	Tick mark if it is available
Application form	
Declaration Letter	
Product Sample	
Specimen of Package including primary label, secondary label and insert	
Initial Registration Certificate (Copy)	

Name and signature of authorized person

Developed By:

Drug Regulatory Authority
Royal Government of Bhutan
P.O Box 1556
Thimphu 11001
Bhutan

Drug Regulatory Authority:
Promoting availability of quality, safe and efficacious medicinal products for consumers

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