GUIDELINES FOR

Obtaining Technical Authorization for Pharmaceutical Manufacturing Plant

1st Edition, 2014

DRUG REGULATORY AUTHORITY
ROYAL GOVERNMENT OF BHUTAN

Revision History

This guideline for obtaining Technical Authorization for Manufacturing Plant is the first version and will be revised from time to time as deemed necessary by the Authority.

Abbreviations and Acronyms

API:	Active Pharmaceutical Ingredient
cGMP:	current Good Manufacturing Practice
GMP:	Good Manufacturing Practices
DRA:	Drug Regulatory Authority
DTAC:	Drug Technical Advisory Committee
FDI:	Foreign Direct Investment
WHO:	World Health Organization
QMS:	Quality Management System
QA:	Quality Assurance
QC:	Quality Control
PIC/S:	Pharmaceutical Inspection Convention/ Co-operation Scheme
Act:	The Medicines Act of Kingdom of Bhutan 2003
Board:	Bhutan Medicines Board
Regulation:	Bhutan Medicines Rules and Regulation 2012
Authority:	Drug Regulatory Authority
Pharmacoepia:	Refers to United States Pharmacopoeia, British Pharmacopoeia, European Pharmacopoeia, Indian Pharmacoepia etc.
Competent Person:	A Competent Person refers to any person who possesses the requisite qualification and practical experience prescribed by the Bhutan Medicines Board and is approved/registered to undertake: a. Manufacture of medicinal products; b. Retail sale of medicinal products; or c. Sale by wholesale trade and distribution of medicinal products
Licensee:	The holder of Technical Authorization for Pharmaceutical Manufacturing Plant

Definition of the terminologies used in this guideline:

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

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

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

d. **g.so-ba-rig-pa medicines**refers totraditional medicines recognized by the Bhutan Medical and Health Council which are manufactured using the ingredients and methods as per the g.so-ba-rig-pa text for intended g.so-ba-rig-pa indication.

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

Acknowledgement

1. Mr. Tashi, Quality Control Incharge, Menjong Sorig Pharmaceuticals, Dept. of Traditional Medicine Services, Ministry of Health (MoH).
2. Mr. Thupten Tshering, Clinical Pharmacist, Pharmacy Dept. JDW National Referral Hospital.
3. Mr. Amin Ngawang Tashi, GovernmentAnalyst, National Drug Testing Lab, Public Health Lab, Dept. of Public Health, MoH.
4. Mr. Jangchhup Peljor, Pharmacist (Procurement Officer), Medical Supplies and Procurement Division, Dept. of Medical Supplies and Health Infrastructure, MoH.
5. Mrs. Ngawang Dema, Sr. Regulatory Officer (GMP Focal Person), Drug Regulatory Authority, DRA.
6. Mr. Kunzang Dorji, Sr. Regulatory Officer (Offtg. Chief Regulator Officer), Registration Division, DRA.
7. Mr. Pelden Chejor, Regulatory Officer (Offtg. Chief Regulatory Officer) Inspection Division, DRA.
8. Mr. Gyem Tshering, Regulatory Officer, Registration Division , DRA.

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Background

The Medicines Act of Kingdom of Bhutan was enacted in 2003.It was followed by the Bhutan Medicines Rules and Regulations in 2005 with subsequent editions in 2008 and 2012. As per Chapter VII section 20.1 of the Act, ***"The Ministry of Trade and Industry shall issue licenses for manufacture, import, export and sale of medicinal products by retail or wholesale based on the approval from the Authority".***

This guideline aims to guide the potential applicants in fulfilling the technical and regulatory requirements of the Technical Authorization for manufacture of medicinal products in accordance to the Chapter VI of the regulation.

As a general guidance, all manufacturing plants are required to conform to the WHO guidance on cGMP; PIC/S Guide to GMP and its relevant annexure; and other standards as set by the Authority.

The assessment of the application for Technical Authorization will be done by the Authority and if required, subject matter expertise will be involved.

Scope

This guideline applies to the Technical Authorization for manufacture of all categories of medicinal products in the country.

Principle Requirements

- The manufacturing plant should be located at a suitable distance from other factories to prevent pollution and contamination.
- The manufacturing plant intending to manufacture biopharmaceuticals or biotechnology medicinal products should have the safety measures against pathogens. It should not pose any risk to the public health and safety.
- Approval from Bhutan Narcotic Control Agency is required for the manufacturing plants intending to manufacture controlled medicinal products falling under schedule C1 (Controlled Narcotic Drugs) and C2 (Controlled Psychotropic substances)of Chapter XV section 249 (c) of the regulation.
- Pre-approval and routine GMP audits will be conducted to assess the conformance of manufacturing plants to GMP standards.
- As per Chapter VII section 21.1 of the Act, the manufacture of medicinal products is required to be carried out under the supervision of a Competent Person approved for the purpose.
- The manufacturing plant should have quality control unit independent from the production unit. The quality control unit should have the laboratory equipped with qualified staff and appropriate equipmentto carryout necessary tests.

General Requirements of the Application

The application and documents should be:

- In English or Dzongkha or both
- Properly bonded
- In A4 size paper
- Be complete as per the specifications detailed in this guideline

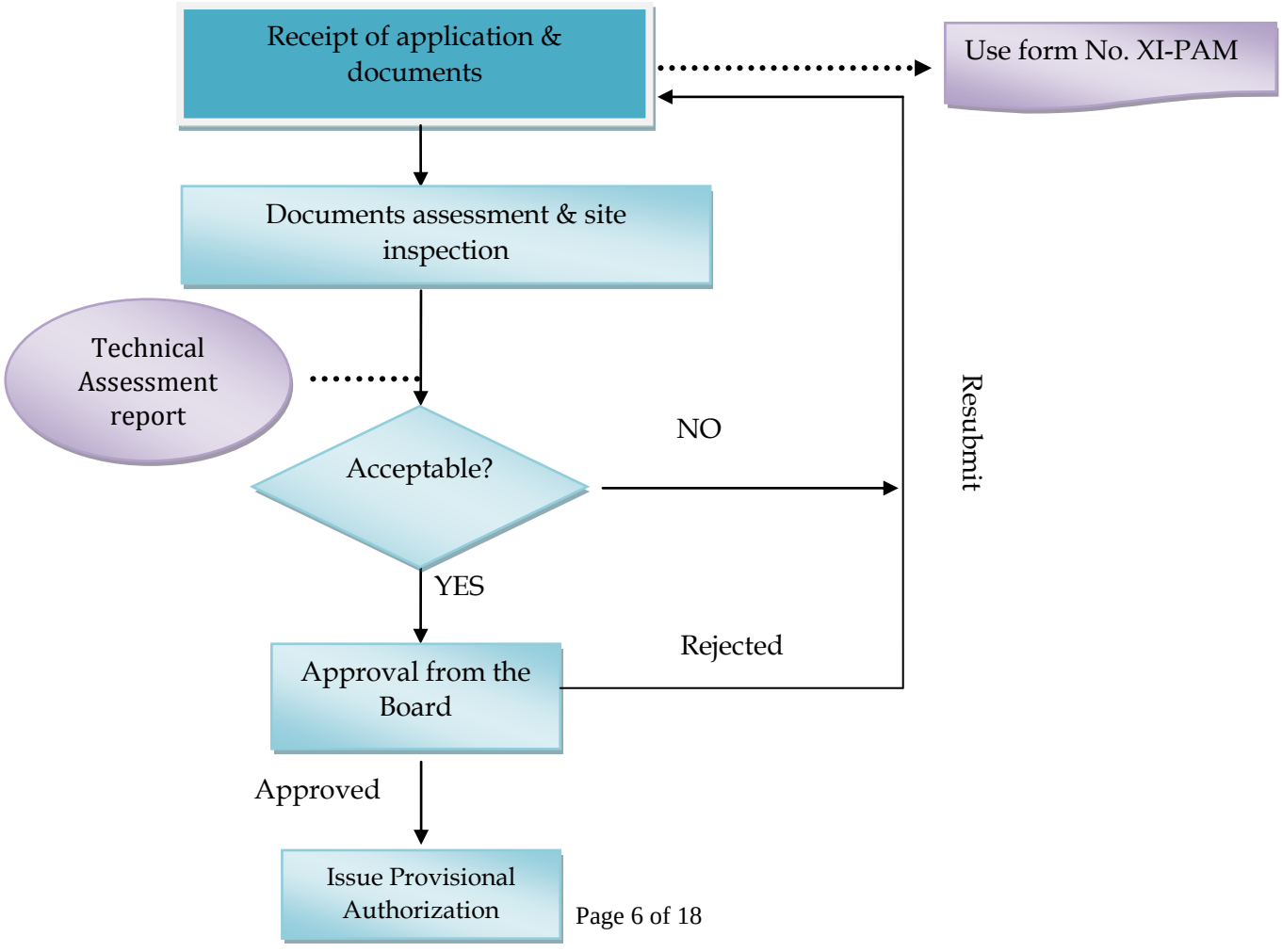
Exemption

In accordance with Chapter VI section 93 of the regulation, the TA for Manufacturing Plantis exempted for dispensing or preparation of extemporaneous formulations/compoundingmeant for treatment in:

- private pharmacies by competent person
- government hospital or dispensary by health professionals registered with Bhutan Medical and Health Council
- veterinary centres by veterinary practitioners registered with Department of Livestock.

Application Procedures for Provisional Technical Authorization to set up Manufacturing Plant

Flow Chart



As per Chapter VI, section 94 of the regulation, any person intending to set up a manufacturing plant should:

- Use the check list attached as *Annexure 1* for preparation of documents.
- Apply to the Authority in duly filled form XI-PAM attached as *Annexure 2* to this guideline.
- Deposit a fee of Nu. 5000 (five thousand only).The fee may be revised from time to time by the Authority.
- Submit complete documents.

Documents should include the following:

a. Name of the proposed manufacturing plant

b. **Proposed site plan**
The plan should include:

- Physical address
- Postal address
- Telephone number and fax number, if available
- Email address of the proponent
- Bird's eye view or the Sketch map
- Pictorial presentation
- The size of the proposed site
- Location and immediate surrounding environment
- Other manufacturing activities on the site, if available

c. Memorandum of Association or Article of Incorporations of the firm
This should include:

- Type of business set up viz, government, private, corporate, Foreign Direct Investment, etc
- List of shareholders in case of corporate and FDIs
- Contractual agreement between the shareholders in case of corporate and FDIs
- Organization chart showing the arrangements for quality assurance, production and quality control
- Short description of the Quality Management System

d. Description and Graphic Layout of the premise
It should include:

- Description of the buildings
- Material, personnel movements and technological order clearly indicated using different legends.
- Management and administration
- Starting material stores
- Packaging material stores
- List of intended Production lay out: Capsule, tablet and other dosage forms manufacturing layout
- Utility unit including HVAC and water system Detail should be given for critical

areas with potential risk of air-borne contamination (schematic drawings of the systems are desirable)
- Classification of the rooms used for the manufacture of sterile products based on risk applications (Eg: sterile products).

e. List of key technical personnel (Production Head, Quality Control, Store In-charge)
The list should include:
- The number of employees in each department
- Qualifications, experience and responsibilities of key personnel
- Outline of arrangements for basic and in-service training and how records are maintained.
- Health and hygiene of the key personnel

f. List of medicinal products to be manufactured
- Types of dosage forms
- Therapeutic category(ies)
- Composition, strength and pharmacoepial/g.so-ba-rig-pa standard of each formulation
- Any toxic or hazardous substances handled e.g., beta lactams, hormones, cytotoxics. Indicate whether the products are manufactured in a dedicated facility or on a campaign basis.
- Human (including g.so-ba-rig-pa medicines) and veterinary products if manufactured on the site.

g. Equipment and machinery
- List and Brief description of major production and quality control laboratories equipment eg. Rotary tablet press, pH meters, Gas Liquid Chromatography, incubators etc.

h. Waste Management Plan(Effluent Treatment Plant)
It should include detailed plan for management of wastes generated from the manufacturing plant.

Procedures for issuing Provisional Technical Authorization

As per Chapter VI, sections 95-102 of the regulation, the following procedures will be followed while issuing Provisional Authorization

a) Upon receipt of the application with complete set of documents, the Authority will :
- assess the application within 30 working days
- inspect and verify the location and the premise site
- provide any observations of deficiencies in writing, including the grounds for refusal and advice for improvement if required for resubmission
- prepare technical assessment report to be submitted to the Board for provisional approval

- issue the Provisional Technical Authorization upon approval by the Board within 10 working days
- Specify the next date of inspection while issuing Provisional Technical Authorization.

b) The Provisional Technical Authorization will:
   - be issued in the prescribed format
   - be valid for two years from the date of issuance or on an earlier date if the applicant applies for final approval for authorization

c) Whilst within the valid period of Provisional Technical Authorization, the applicant should submit the revised or additional documents for obtaining approval of any changes:
   - for inclusion of new medicinal products under the same therapeutic category
   - in the layout of the premise

d) The applicant should submit a new application in case of the following major changes including change in:
   - location
   - formulation
   - therapeutic category
   - facilities and equipment
   - operation and process

If the above changes are requested to the Authority during the valid period of Provisional Technical Authorization, the application fee is not required. However, the Authority reserves the right to approve the proposed changes.

e) The Provisional Technical Authorizations not a substitute for Technical Authorization issued by the authority and Manufacturing License issued by the Ministry of Economic Affairs.

f) The Authority reserves the right to revoke or cancel the Provisional Technical Authorization in the following cases:
   - deviations from the proposed technical layout
   - any unapproved changes under part (c) and (d) of this guideline

Renewal of Provisional Technical Authorization

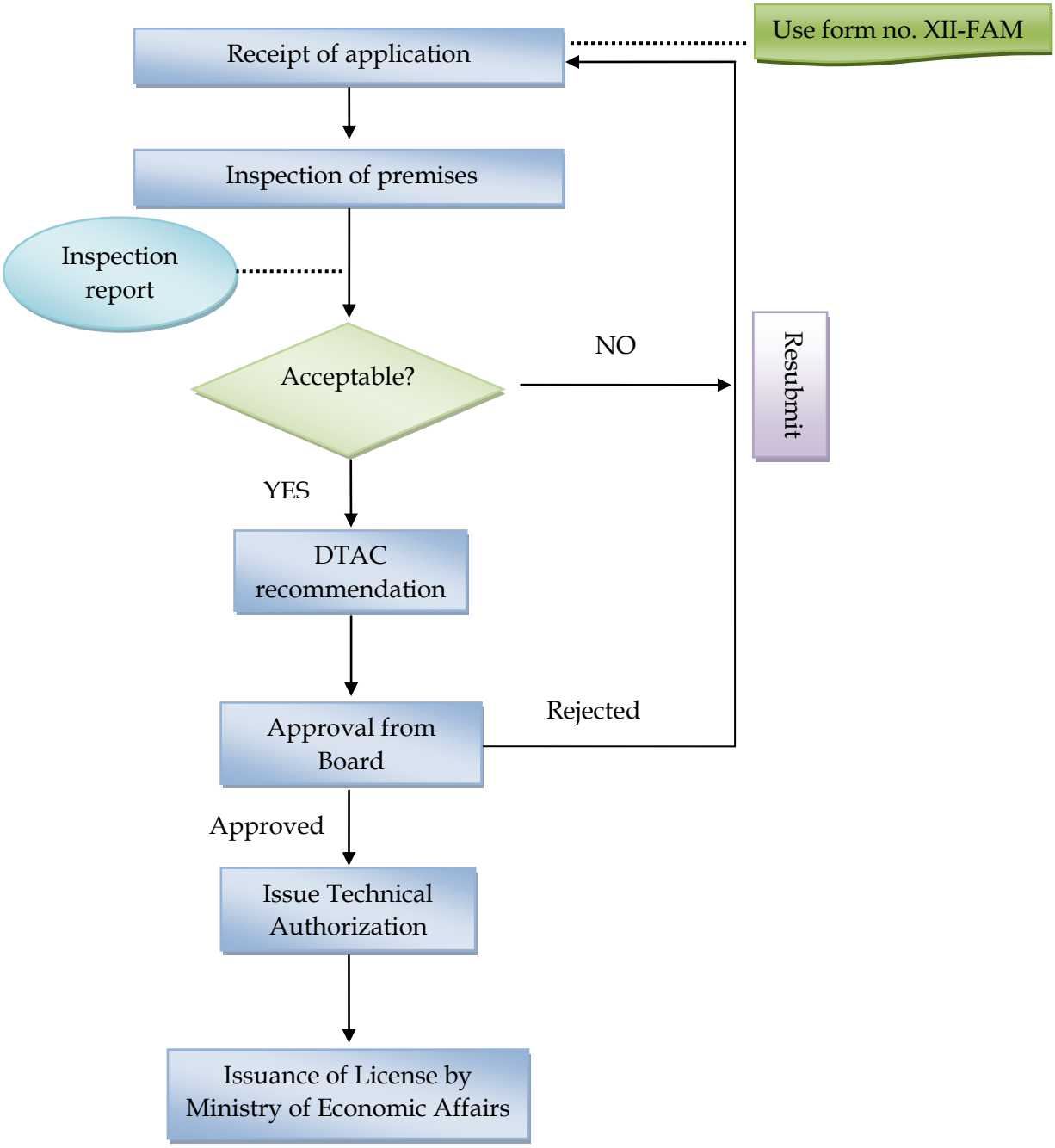
As per Chapter VI, section 103 of the regulation; the following procedures will be followed while applying for renewal of Provisional Technical Authorization:

- Application for renewal should be submitted in form XI-PAM (same form as that used for new application)
- The application must be made at least 30 days before the expiry date of Provisional Authorization.
- The application must be accompanied by renewal fee of Nu. 500.00(Five Hundred)
- A grace period of three months may be given if a written justification with evidence of having carried out the renewal process prior to the date of expiry is submitted.

- In case of failure to provide the evidence during the grace period, the Provisional Technical Authorization will be deemed cancelled or revoked from the actual expiry date. The application will be considered new if the Provisional Technical Authorization has been cancelled.

Approval for Technical Authorization

Flow Chart



In accordance with Chapter VI, section 104-109 of the regulation; the following procedures will be followed for obtaining Technical Authorization:

a) Once the premise or facility is ready, the applicant should:

- apply to the Authority in duly filled form XII-FAM attached as *Annexure 3*
- deposit a fee of Nu. 5000 (five thousand only).The fee may be revised from time to time by the Authority.

b) Upon receipt of the application, the Authority will:

- Inspect the facilities to verify GMP as per the PIC/S, WHO standard and any other relevant standards as set by the Authority.
- Provide any observations of deficiencies in writing, including the grounds for refusal and direction for further improvements.
- Submit inspection report to the DTAC for recommendations after rectification
- Submit the inspection report along with the recommendations of DTAC to the Board for approval of Technical Authorization.
- Issue the Technical Authorization upon approval by the Board within 10 working days.

c) The Technical Authorization will be:

- issued in the prescribed format
- valid for one year from the date of issue
- a pre-requisite for trade license which is issued by the Ministry of Economic Affairs

Renewal of Technical Authorization

As per Chapter VI, section 110 of the regulation; the following procedures will be followed while applying for renewal of Technical Authorization:

- Application for renewal shall be submitted in form XII-FAM (same form as that used for new application).
- The application must be made at least 30 days before the expiry date of Technical Authorization.
- The application must be accompanied by renewal fee of Nu. 500
- A grace period of three months may be given if a written justification with evidence of having carried out the renewal process prior to the date of expiry is submitted.
- In case of failure to provide the evidence during the grace period, the Technical Authorization will be deemed cancelled or revoked from the actual expiry date. Once cancelled, the application will be considered new wherein Provisional Authorization for Manufacturing Plant must be first obtained.

Responsibility of the Licensee

The licensee is responsible for:

- All the information supplied in support of his application for Technical Authorization.
- Updating any information relevant to the application.

- Providing unhindered access to inspection.
- Overall compliance to the regulation and standards set by the Authority.

Processing of the Application

1. Initiation of Review

Review of applications will follow a queue system.

2. Stop Clock

- The clock starts once payment has been confirmed for a submitted application and will stop whenever the Authority needs to seek further information from the applicant. The clock restarts when the Authority receives complete responses from the applicant.
- A period of three (3) months will be given within which the applicant should submit the additional information/clarification required for each correspondence from the Authority.
- The clock stops when the Authority informs the applicant of its regulatory decision.

3. Rejection of the application

- An application for Provisional or Technical Authorization will be rejected in following cases if the applicant fails to:
  - Respond to the enquiries or submit the required additional documents within three (3) months from the last correspondence date. ***OR***
  - Submit all the required documents and complete the authorization formalities within six (6) months from the date of application.

- Once the application is rejected, the applicant will be informed and the documents will be handed over.

- To re-process the application, the applicant must re-submit the complete set of documents along with the application fee. The application will be treated as new.

Regulatory Decisions

1. Decisions of the Authority

Regulatory decision will be made based on the outcome of the assessment of documents and report of the site inspection. The decision will be accordingly communicated to the applicant.

2. The Provisional and Technical Authorization will be issued in a specified format

3. Rejection, Suspension or Cancellation

The Board may reject, suspend or cancel the Provisional Technical Authorization or Technical Authorization, if the applicant fails to comply with conditions laid down in the regulation.

4. Appeal

Any applicant aggrieved by the regulatory decisions may submit a written petition to the Board within thirty (30) days from the date of issue of the decision as per chapter XVII of the regulation.

Cancellation of Technical Authorization

The Authority may, in the interest of public safety, reject or cancel the Technical Authorization if:

- Any of the conditions of Technical Authorization has been contravened. This may include the mismatch of the documents submitted during the application and field GMP audit
- Any serious non-compliance reports have been received from GMP audit or any other external audits;
- The licensee obstructs the inspection of the manufacturing firms or premises; Or
- For any other matters as specified by the Board at the time of cancellation.

Transfer of Technical Authorization

1. The Technical Authorization may be transferred to another individual or firm authorized by the Authority, upon fulfillment of the following:

- An application to transfer the Technical Authorization should be submitted by the proposed licensee.
- The current licensee agrees to surrender the existing authorization and issue statement of no objection for transfer of Technical Authorization to the proposed licensee.
- The existing Technical Authorization should have a remaining validity period of at least one (1) month. If the period is less than one month, the Technical Authorization should be renewed by the existing licensee before the transfer application is submitted.

2. Once the Technical Authorization has been transferred, the new licensee will be responsible for all matters relating to the manufacture of products and product performance.

3. No fee will be charged for the application and the outcome of the transfer application will be notified to both the existing and new licensee.

Annexure 1: Checklist for submission of documents for Provisional Technical Authorization (Tick if you have included in the Dossier)

Document	Tick appropriate one			Remark
	YES	NO	Not applicable	
Name of the proposed ***Manufacturing Plant***				
Dully filled application form (XI-PAM)				
Application fee				
Postal Address of the proposed site				
Sketch Map or Bird's eye view of the proposed site				
Organization chart				
List of shareholders				
Contractual agreement				
Brief description of Quality Management System				
Description and Graphic Layout of Premises with details of production, material and personnel movement				
Brief Description of HVAC and water systems				
List of key Technical Persons (Production, Quality control, Store)				
Training program				
Personnel Hygiene Requirement				
List of Medicinal Products indicating the formulation, composition, strength, dosage form, pharmacopoeial standards				
Brief information of equipment and machinery for manufacture and testing				
Waste Management Plan				

Annexure 2: Application form for Provisional Technical Authorization

Form: XI-PAM
Regulation Section: 94 & 103

APPLICATION TO SET UP A MANUFACTURING PLANT FOR MEDICINAL PRODUCTS

I/we .....of..... hereby apply for the grant/renewal of a provisional authorization to set up a manufacturing plant for medicinal products, and I have attached the following documents

a. *Location of the proposed site with pictorial presentation or sketch map of the proposed factory site plan,*
b. *Memorandum of Association or Article of Incorporations of the firm including organizational chart,*
c. *Graphic Layout of the premise detailing on the intended production facilities and traffic routes for material and personnel,*
d. *Description of the layout of the premise,*
e. *List of key technical personnel (Production head, Quality Control, Store In-charge),*
f. *List of Medicinal Products indicating the formulation, composition, strength, pharmacopeial specifications intended to be manufactured,*
g. *List of equipments and machinery to be employed for manufacture and testing, and*
h. *Waste management plan(Effluent Treatment Plant)*

The Plant is expected to be operation with effect from.....

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

Declaration (please tick the boxes):

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

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

Signature of applicant:
Name & address:

Date: .....

Annexure 3: Authorization for Provisional Technical Authorization

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Drug Regulatory Authority
Royal Government of Bhutan

Regulation No.: 96

PROVISIONAL AUTHORIZATION TO SET UP A MANUFACTURING PLANT FOR MEDICINAL PRODUCTS

No.: .....

M/s ..... is hereby authorized to institute the manufacturing facility provisionally for manufacture of the following products on the premises situated at .....

Sl. No	Product Name	Pack	Composition (With Strength)

The authorization shall be in force from ..... to ..... for a period of two years or till the grant of approval for manufacturing license whichever comes first.

Next date of inspection:

Conditions:

The authorization is subject to the conditions stated below and to such other conditions as may be specified in the Bhutan Medicines Regulations.

i. The applicant shall not manufacture during the provisional authorization until authorized with final approval by the Authority.
ii. The applicant shall not deviate any technical specifications as approved during the provisional authorization without seeking approval from the Authority.

This registration Certificate is granted vide application dated ..... of M/s .....

Signature and Seal
Drug Controller

Date:.....

Annexure 4: Application form for Technical Authorization

Form: **XII-FAM**
Regulation Section: **104 & 110**

APPLICATION FOR TECHNICAL AUTHORIZATION FOR MANUFACTURE OF MEDICINAL PRODUCTS

I/we .....of..... hereby apply for the grant/renewal of authorization to manufacture the medicinal products as the following firm is ready for production;

Name of the firm:
Location/Address of the firm:

Provisional Authorization no.:
(*As issued by DRA*)
Expected dated of Operation:
(*If different from what was indicated on the Provisional Authorization application*):
Name of the Proposed Competent Person(s):
Production Manager:
Quality Assurance Manager:
Store In charge:

List of standards or Operating procedures:
(*Please use additional sheet*)

The prescribed fee been deposited to the Royal Government of Bhutan vide Revenue Receipt No..... (Please attach copy)

Declaration (please tick the boxes):

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

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

Signature of applicant:
Name & address:

Date: .....

Annexure 5: Application form for Technical Authorization

སྨན་རིགས་ཀྱི་ལས་གཞི་དབང་འཛིན།

Drug Regulatory Authority
Royal Government of Bhutan

Regulation Section: 107

AUTHORIZATION FOR MANUFACTURE OF MEDICINAL PRODUCTS

No.: .....

M/s ..... is hereby authorised to manufacture the following products on the premises situated at ..... under the direction and supervision of the following competent person(s):

(a) Production Supervisor: .....
(b) Quality Assurance Manager: .....
(c) Store In-charge: .....

Sl. No	Product Name	Pack	Composition (With Strength)

Conditions of license:

1. The licensee shall inform the Authority in writing in case of any change in the Competent Person(s) and in the premises and ownership of the firm.
2. No drugs other than those in the approved list shall be manufactured.
3. The manufacturing of the drugs shall be carried by the Competent Persons in line with the existing Bhutan Medicines Rules and Regulations.
4. The licensee shall not manufacture drugs during the period of suspension of license.

This registration Certificate is granted vide application dated ..... of M/s .....

Signature and Seal
Drug Controller

Date: .....

References:

The following books/documents were used as sources of information in the preparation of this guideline.

1. The Medicines Act of the Kingdom of Bhutan 2003
2. Bhutan Medicines Rules and Regulation 2012
3. PIC/s guideline document
4. WHO guidance document

Drug Regulatory Authority:
Towards promoting consumers' confidence in the medicinal products

Contact Details:

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