Manufacturing of Medical Products in Bhutan

Guidance Document on Technical Authorization for Manufacture and Regulatory Certifications.

DRA-G-D1-TA-08

Drug Regulatory Authority

TECHNICAL AUTHORIZATION FOR MANUFACTURE

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Abbreviations and Acronyms

API:	Active Pharmaceutical Ingredient
Act:	The Medicines Act of Kingdom of Bhutan 2003AHU:
AHU:	Air Handling Unit
Board:	Bhutan Medicines Board
CoPP:	Certificate of Pharmaceutical Product
GMP:	Good Manufacturing Practice
DRA:	Drug Regulatory Authority
DoI:	Department of Industry
DTAC:	Drug Technical Advisory Committee
FDI:	Foreign Direct Investment
GxP:	"Good practice". "x" stands for the various fields
HVAC	Heating Ventilation & Air Conditioning
MoEA	Ministry of Economic Affairs
QA:	Quality Assurance
QC:	Quality Control
QMS:	Quality Management System
PIC/S:	Pharmaceutical Inspection Convention/ Co-operation Scheme
Regulation:	Bhutan Medicines Rules and Regulation 2012
WHO:	World Health Organization
NEC:	National Environment Commission

1. Introduction

As per the Medicines Act of the Kingdom of Bhutan 2003, Drug Regulatory Authority (DRA) is empowered to regulate medicinal product to ensure that the pharmaceutical products meet appropriate standards of safety, efficacy and quality. Product market authorization, pharmacy licensing, post marketing surveillance including manufacturing inspections are the key activities of DRA.

In accordance to National Drug Policy 2007, Government shall promote and support local manufacture of pharmaceuticals in order to promote self-sufficiency. The policy also mandates DRA to develop and enforce guidelines on manufacture such as but not limited to Good Manufacturing Practices (GMP), Good Clinical Practice (GCP), and Good Storage Practice (GSP). Bhutan Medicines Board, empowered by the Medicines Act has the authority to approve any production related to medicinal products, hence technical clearance from DRA is a pre-requisite for the manufacturing license which is granted by the Ministry of Economic Affairs. As per the instruction from the 17th Bhutan Medicines Board meeting, DRA is to propose clear policies to prioritize the type of pharma and medical products' industries based on possible benefit to the country including import substitution, use of locally available raw materials, and economic benefits.

With the listing of "Manufacture of Pharmaceuticals" under the priority List of activities in the Foreign Direct Investment (FDI) Policy of Bhutan, DRA is in receipt of applications from manufacturers. A guidance document is found necessary to guide the applicants on the policy, procedures and conditions for proposing to manufacture in Bhutan and encourage transfer of technology in pharmaceutical sector in a manner compatible with the country's needs. Although there are international standards for Good Manufacturing Practices (GMP), it is only imperative that we draw some country specific regulatory requirements to create a better understanding between the proponent and the regulator.

Since the policy is directed towards promoting the growth of the local pharmaceutical industry, the role of regulatory agencies must also set clear procedures to create an environment conducive to channelizing a higher level of investment into pharmaceuticals. On the other hand, local domestic market being very small, the manufacturers must target for international market and in order to achieve this, the manufacturers must maintain appropriate manufacturing standards in an internationally competitive market.

This document is prepared with the aim 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

Medicines regulation and also for promoting uniformity and transparency in making the regulatory decisions. The requirements in this guidance document have been drawn from international sources such as the World Health Organization (WHO), the Pharmaceutical Inspection Cooperation/Scheme (PIC/S), scientific associations and other regulatory agencies in the region. The document contains two parts; namely part I and II. Part I contains "General Requirements, conditions and process for obtaining clearance for setting up the Manufacturing Authorization for medical products" and Part II contains "Specific requirements for manufacture of the Medical products". Further, for the purpose of clarity, it explains both the regulatory conditions and procedures for manufacture of the medical products right from screening of the proposals, conditions for acceptance and process involved in certifications and conditions for cancellation of the authorizations.

However, this guidance does not specify what information should be included as a part of a regulatory submission for product registration and the GMP requirements for specific products that are covered by separate guidelines. In the event of failing to cover all possible cases, such ways of complying with GMP regulations are to be considered with proper scientific justification based on the international practices, references from WHO, PIC/S, ICHs and sources from other international regulatory bodies. This document may be updated as and when required depending upon the needs and changes to the national and international regulatory norms.

1.1 Objectives

i. To assist the applicants in preparation of the proposal, to understand the conditions for setting up a manufacturing plant
ii. 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 Medicines regulation.
iii. To provide the conditions and process for obtaining regulatory certifications(GMP, CoPP, Free Sale certificates)
iv. To provide guidance to Drug Regulatory Officials for enforcing the rules in fair, consistent and effective manner.

1.2 Scope

This Guideline shall apply to following category of Medical products right from the screening of the proposal till final approval for manufacture. It also states conditions for certification, renewal processes and cancellation of the authorization:

i. Pharmaceuticals

ii. Active Pharmaceutical Ingredients
iii. Traditional or Herbal Medicinal Products
iv. Veterinary medicinal products/vaccines
v. Medical devices (Medical syringes and Sterile disposable perfusion and blood collection sets,
vi. Medical gases

This guidance does not cover the following types of products:

i. Health supplements
ii. Human tissues intended for transplantation

2. Definition of the terminologies used in this guideline:

i. **Authority or DRA** refers to Drug Regulatory Authority
ii. **Active Pharmaceutical Ingredient** (API) refers to Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.
iii. Airlock refers to an enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods (PAL, Personnel airlock and MAL, Material airlock).
iv. **Campaign Production** means manufacturing of a product in row with use of equipment with proper cleaning validation.
v. **Competent Person** refers to any person who possesses the requisite qualification and practical experience and is approved/registered to supervise the manufacture/testing of medicinal products.
vi. Cleanroom refers to a room or area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.
vii. **Critical deficiency** refers to non GMP conformity posing high risk on the quality of the products, it will bear the same meaning as per the GMP Inspection report.
viii. **Contamination** refers to the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

ix. **Cross-contamination** means contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

x. **Dedicated Facility** is defined as Facility within same building with no common access and with separate HVAC and having common Utilities and Waste treatment. It may be in the same floor or may be in different floor.

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

xii. **Formulations** refers to finished pharmaceutical products available in various dosage forms.

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

xiv. **Hazardous Product** refers to substances having high risk to the human health due to its chemical nature such as certain hormones, steroids or cytotoxins, penicillin, cephalosporin, sex hormone.

xv. **Hazardous waste** means a waste (a) which because of its quantity, concentration, persistence or physical, chemical or infectious characteristics may cause or significantly contribute to an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness, or pose a substantial present or potential hazard to human health or the environment when improperly treated, stored, transported, or disposed of, or otherwise managed and (b) belong to any of the categories listed in Annexes to the regulation on hazardous as per Waste Prevention and Management Regulation 2012

xvi. **Immediate/Primary packaging** means container or other form of packaging, which is immediately in direct contact with the medicinal product

xvii. **ISO 13485:2016** is an internationally recognized quality standard which states the requirements of the Quality Management System (QMS) for the design and manufacture of Medical Devices throughout the world.

xviii. **Labelling** means the information contained on the immediate or outer packaging;

xix. **Licensee** refers to the holder of Technical Authorization for Pharmaceutical Manufacturing Plant

xx. **Market Authorization** refers to product registration.

xxi. **Medical devices** refer to "Any article, instrument, apparatus or machine that is used in the prevention, diagnosis or treatment of illness or disease, or for detecting, measuring, restoring, correcting or modifying the structure or function of the body for some health purpose". Accordingly, the medical equipment also falls under the scope of this regulatory control provided that the equipment is utilized directly or indirectly for the above mentioned health purpose.

xxii. **Medical Device Classification** refers to international categorization of medical devices into one of the following classes based on perceived risk of the device to the patient or user.
Class A - Low Risk
Class B -Medium Risk
Class C- Higher Risk
Class D- Highest Risk

xxiii. **Medical Products** 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 including vaccines and biologicals; and it includes medical devices and diagnostics.

xxiv. **Medicinal gases** refer to gases that is manufactured, packaged, and intended for administration to a patient in anesthesia, therapy, or diagnosis.

xxv. Multination companies(MNC) is defined as follows:

i. The company having establishment in one of the developed countries as defined under the UNDP and World Bank; OR
ii. Company with multiple establishments with one of the establishment in a developed country; OR
iii. The product of which is globally available and registered with at least 2 referenced NRA;OR
iv. The company in top 10 list in stock exchange of developed countries as per World Federal of Exchange available at http:www.world-exchanges.org/ststistcs/monthly-reports OR

xxvi. The company with its manufacturing site in developing country and co-owned by at least 2-3 different nationals.**New dosage form** refers to a pharmaceutical product which is a different pharmaceutical product type, but containing the same active substance. Such pharmaceutical product types include products of a different route of administration (e.g. oral to parenteral), new specific functionality/delivery systems (e.g., immediate release tablet to modified release tablet) and different dosage forms of the same route of administration (e.g. capsule to tablet, solution to suspension).

xxvii. **New Product** means non-pharmacopeial product, or In-house products approved by minimum of two NRAs.

xxviii. **Packing** refers to an act of dividing a bulk into small quantities and filling in a unit pack and subsequently sealing, labeling and packaging.

xxix. **Package** insert means a leaflet containing information for the prescriber and the dispenser

xxx. **Pharmacopeia** refers to United States Pharmacopoeia, Japan, British Pharmacopoeia, European Pharmacopoeia, Indian Pharmacopeia and International Pharmacopoeia.

xxxi. **Plant layout** refers to the most effective physical arrangement, either existing or in plans of industrial facilities i.e. arrangement of machines, processing equipment and service departments to achieve greatest co-ordination and efficiency of 4 M's (Men, Materials, Machines and Methods) in a plant.

xxxii. **Production** refers to all operations involved in the preparation of a pharmaceutical product, from receipt of the starting materials, through processing and packaging, to completion of the finished product

xxxiii. **Provisional Authorization** refers to principle approval accorded to the proponent to initiate the construction or setting up a manufacturing plant.

xxxiv. **Quality System or Quality Management System (QMS) refers to** a formalized system that documents processes, procedures, and responsibilities for achieving quality policies and objectives (it actually refers to the entirety of the system).

xxxv. **Quarantine** refers to the status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing

xxxvi. **Referenced NRAs** means any National Regulatory Agency with similar functions that of DRA and recognized by DRA for the purpose of regulatory controls and reliance. This shall have same meaning in the Medicines Regulation.

xxxvii. **Self-contained area refers to dedicated premises** which provide complete and total segregation of all aspects of an operation, including personnel and equipment movement, with established procedures, controls and monitoring. This includes physical barriers as well as separate air handling systems, but does not necessarily imply separate buildings.

xxxviii. **Separate facility** refers to a totally dedicated and self-contained building which is isolated from other buildings in the site.

xxxix. **Outer /Secondary packaging** means the packaging into which is placed the immediate packaging;

3.0 General requirements and Conditions

Any manufacturing facility shall fulfill the following basic requirements in order to obtain the technical authorization;

3.1 The approval or authorization from Authority is prerequisite for obtaining manufacturing license for any medical product.

3.2 The Authorization for manufacture involves three stages of review by the Authority, Viz. screening of the proposal for the manufacture; review of the Plant layout and; and facility inspection for final approval for operationalizing the plant.

3.3 If the initial proposal is acceptable to the Authority, only then the applicant is required to submit the detail plan layout for the Provisional Authorization to construct a manufacturing factory.

3.4 Upon receipt of Provisional Authorization, the applicant shall process for environmental clearance as per the Environmental Assessment Act 2000 and its corresponding regulation.

3.5 The applicant should get approval of layout design of the proposed manufacturing premises prior to initiation of any construction.

3.6 For the operational authorization (Final Authorization for manufacture), the premise shall be completed as per the approved layout and ready for implementation of the quality system that incorporates good manufacturing practices (GMP).

3.7 Factory sites shall be situated in sanitary locations at a sufficient distance from other factories with the potential risk of contamination, fires and safety measures.

3.8 Once the pharmaceutical/medical product factory site has been approved, the relevant authority (viz. MoEA, Thromde etc.) shall ensure that no approval is provided for establishing factories with risk of potential contamination from and/to the immediate environment in the proximity of same area or site.

3.9 Factory buildings shall be solid and safe, and designed to prevent rodents, insects and dust; interior ceilings, walls and floors shall be smooth and free of cracks and crevices, easy to clean, and non-conducive to the collection of dust.

3.10 Factory buildings shall be well constructed and safe; manufacturing, processing and packaging areas shall be completely separated from offices, reception rooms, laboratories, restaurants and their associated lavatories; the use of asbestos shall be avoided.

3.11 There shall be facilities for the treatment of dust and powder, wastewater, hazardous wastes, toxic containers, hazardous gases, biological components and other hazardous components or materials.

3.12 There shall be appropriate lavatory facilities in manufacturing and processing areas but these areas shall not lead directly to the manufacturing and storage areas.

3.13 Maintenance workshops shall be separate and away from production areas.

3.14 Areas housing animals for experimental tests shall be isolated from other areas.

3.15 Outsourcing any type of the service related to manufacture (viz. quality control activities, research and development, processing stages, packing etc.) of the products shall be scientifically or logically justifiable.

3.16 The applicant industry should have its own full-fledged testing laboratory. Only one or two tests which are not regularly done and not feasible due to high cost may be carried out from accredited laboratory with formal contract.

3.17 The head of the Quality Control Laboratory shall be independent of the manufacturing unit. The testing shall be conducted under the direct supervision of competent technical staff who shall be whole time employees of the licensee.

3.18 Equipment used in the manufacture, processing, packing or holding of an active pharmaceutical ingredient shall be of appropriate design, adequate size and suitably located to facilitate operations for its intended use and for its cleaning and maintenance. All equipment must be brand new (i.e. not secondhand) as required by the NECS.

3.19 For hazardous gases and dust, airtight facilities, local exhaust ventilation systems and negative pressure procedures shall be established; these substances shall, in accordance with their properties, be scrubbed, collected, oxidized, reduced, combusted, or otherwise appropriately treated. If exhaust gas contains dust, it shall first be subjected to centrifuging, filtering, scrubbing, or some other form of dust-removal processing; the emission of such gases must comply with air pollutant emission standards.

3.20 For hazardous waste materials and toxic containers, storage facilities shall be established, and these materials and containers shall be decomposed in accordance with their properties, and then appropriately incinerated or buried. If toxic containers are to be reused, they shall be washed and rigorously controlled, and may not be used to hold food products.

3.21 For the processing of wastewater, impermeable storage pools shall be established, and acidification, alkalization, neutralization, active carbon adsorption, or other effective methods shall be used to break down or remove wastewater toxins; the release of wastewater must comply with Environment release standards.

3.22 Sites and facilities for the manufacturing of pharmaceuticals for human and animal use shall be kept separate; they may not be operated in the same building without separation. However, pharmaceuticals for animal use that comply with the standards governing drugs for human use are not subject to this restriction.

3.23 Manufacturers shall have appropriate facilities and equipment being installed depending on the type of the products intended for manufacture.

3.24 Critical instruments used for measuring, weighing, recording and controlling equipment shall have specific calibration periods using appropriate validated methods.

3.25 The Plant layout for setting up any manufacturing plant shall fulfill the following:

i. The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) to ensure that the designation and conditions of use of all the rooms are correctly shown.

ii. The detail plant layout shall be prepared and signed by a qualified & competent firm or personnel who have knowledge on design control for the particular industry. These personnel involved in preparing the plant lay out shall be either certified by competent authority for registering professionals or with adequate relevant experiences supported by biodata.

iii. The person or firm responsible for preparing such as engineering design jobs should be mentioned and signed thereof to take charge and responsibility of ensuring compliance with the state of art pharm.

iv. The specific areas mentioned under specific products shall be assessed on the Layout and any deficiencies or queries shall be communicated.

v. Process area should be demarcated in line with process steps and flow and should be sufficient to carry out the intended process(s).

vi. The proponent is expected to present the plans (2D/3D) for their facilities, company's proposed activities and the approximate timeline for commencement of operations for review by the Authority. The plans must be at a reasonably advanced stage and presented as engineering drawings.

vii. The site visits by the Authority maybe conducted if deemed necessary at the time of review of the layout.

3.26 The manufacture shall be conducted under the direct supervision of competent technical staff with prescribed qualifications and practical experience in the relevant products.

3.27 The key personnel (production manager and Quality Control Manager) possessing suitable qualifications to be engaged in the production and testing respectively shall be registered with the Authority.

3.28 The manufacturer shall employ adequate number of personnel employed in direct proportion to the workload.

3.29 The manufacturer shall ensure in accordance with a written instruction that all personnel in production area or into Quality Control Laboratories shall receive training appropriate to the duties and responsibility assigned to them.

3.30 The production of sterile preparations should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency.

3.31 For sterile preparations, the various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilization should be carried out in separate areas within the clean area.

4.0 Application process for manufacture

4.1 The flow of process for manufacturing authorization is shown in figure 1 while the process for inclusion of any additional products or changes and renewal is shown in figure 2.

4.2 The applicant may apply directly to DRA for technical Authorization. However, in case of FDIs where foreign investors are involved, the application for technical clearance shall be routed through the Department of Industry, Ministry of Economic Affairs.

4.3 The Authorization for manufacture involves three stages of review;

i. Screening of the proposal for the manufacture;
ii. Review of the plant layout for according principle Approval/provisional authorization for setting up the manufacturing plant; and
iii. Facility inspection for final approval for operationalizing the plant or manufacturing the medical products.

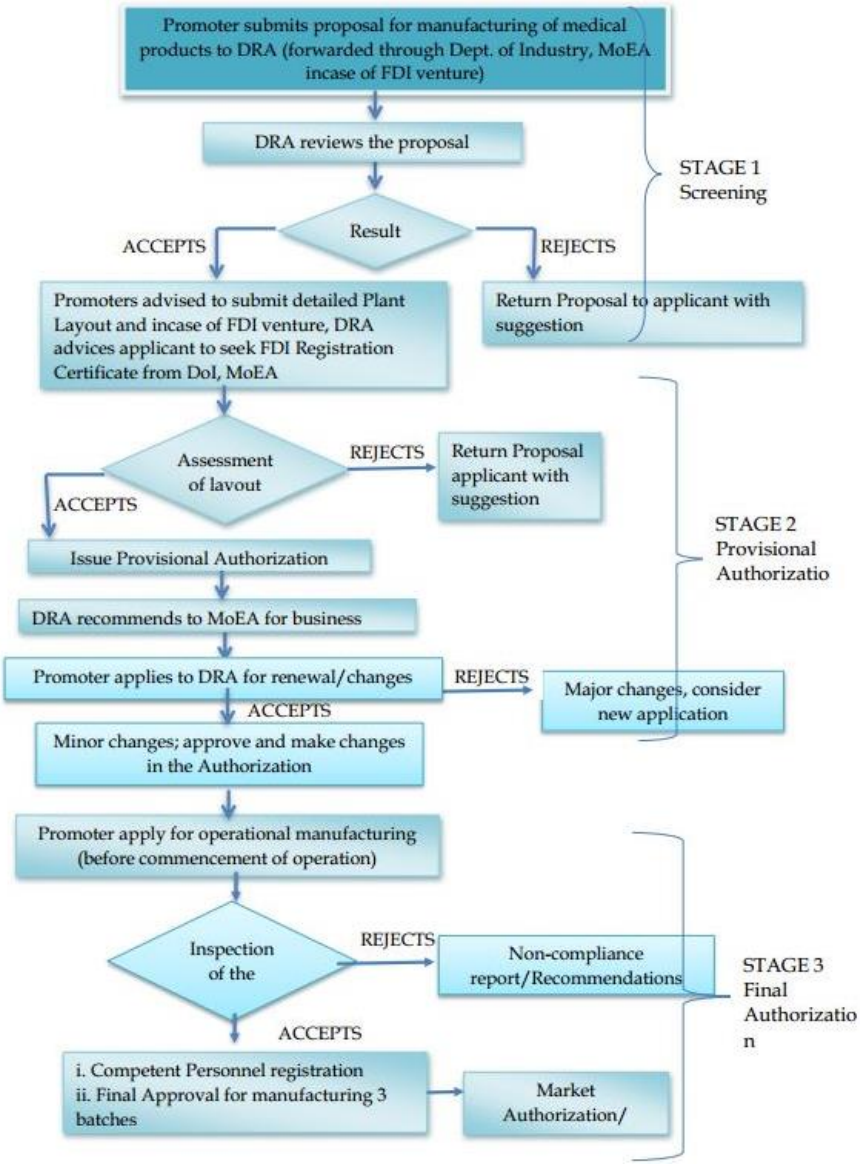

Figure 1: Process flow for manufacturing authorization

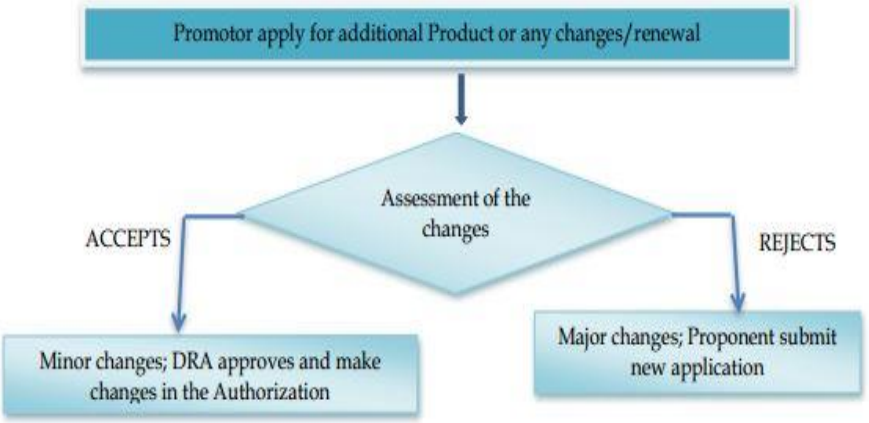

Figure 2: Process for inclusion of any additional products or changes and renewal

4.4 The initial proposal shall contain following details in a specified format (annexed).

i. Front Page (Title, Physical address, Postal address, Telephone number and fax number, if available and Email address);
ii. Introduction of the project with scope of activities;
iii. Objectives of the project;
iv. Source of raw materials;
v. Target Market (mention the intended countries if for export);
vi. Promoters details;
vii. In case of FDI, details of foreign investor/partner;
viii. Technology collaboration if any (mandatory in case of FDI);
ix. Proposed site detail - Bird's eye view or Sketch map/Pictorial presentation, size of the proposed site, location and immediate environment and other manufacturing activities on the site, if available). The layout design of the proposed manufacturing area should be appended with site plot, covered/uncovered land area ratio, activities being conducted in adjoining areas and environmental aspects;
x. Technical Aspects - Brief description of the Quality Management System, arrangement on production and quality control activities (mention any services to be outsourced), Engineering and maintenance, Project Management, type of products intended for manufacture with therapeutic categories, list of intended manufacturing equipment to be procured, intended size of the employees; and
xi. Waste Management Plan - Detailed plan for management of wastes generated from the manufacturing plant.

4.5 The proposal shall be presented to the Bhutan Medicines Board for approval or DRA shall seek clearance through the Chairman, Bhutan Medicines Board. If the proposal is approved for further scrutiny, the Authority shall make a request to the proponent through writing for submission of the detail plant layout.

Screening of the proposal

4.6 The proposal shall be assessed by the Authority keeping in mind of the following criteria and conditions:

4.6.1 Type of medical products intended for manufacture;

i. National Essential medicines list or the formulations including drugs for the neglected diseases as determined by the Drug Technical Advisory Committee will be under the priority list but will not be the reason for the disapproval of other medicines proposed for the manufacture.

ii. Pharmacopeial product including API will be permitted for manufacture.

iii. In case of non-pharmacopeial products, with In-house specifications, the products shall be approved for manufacture provided it is approved by minimum of two NRAs.

iv. Human Vaccines and new molecules for manufacture shall only be approved if it involves Technology collaborations involving Multi-National Companies since it requires deep knowledge on science and technology skills and clinical trials and other resources required for developing new chemical entities.

4.6.2 Technology collaborations;

i. Technology collaborations involving Multi-National Companies are preferred as important channels for the technology competence building.

ii. For FDI proposals, the technical collaboration with established manufacture of similar products (products registered with NRA of country of origin) shall be made mandatory.

4.6.3 Type of Quality System;

i. ISO 13485 Quality Management System for Medical devices;

ii. Good Manufacturing Practice (GMP) standards equivalent to WHO, PIC/S or ICH will be approved for both pharmaceuticals and API.

iii. For veterinary vaccines, ASEAN standards for good manufacturing practices (GMP) for animal vaccines or any standards equivalent to PIC/S or standards published by OIE.

4.6.4 Stages of Manufacture;

Packaging shall only be approved if there is value addition of the product or on the condition that all the manufacturing starting from raw materials shall be carried out in the agreed time line. The details

of the "value addition" could be determined by the DRA in consultation with Department of Industry, MoEA from time to time.

4.6.5 Sources of Raw materials;

i. For Traditional or Herbal medicines, additional clearances from Ministry of Health and Ministry of Agriculture and Forests shall be required to ascertain the availability of natural resources/medicinal plants.

ii. Use of locally available resources for both modern and Traditional/Herbal medicines shall be encouraged.

4.6.6 For medical devices;

i. Approval for lower risk category for medical devices (i.e Class A and B) category of products may be allowed without any external technical collaboration.

ii. For products falling under higher categories (i.e class C and D), approval may be accorded only if there is collaboration with established manufacturers for similar products outside the country and/or their product being registered/listed in referenced NRAs.

4.6.7 Market;

i. The products intended for both domestic and international market will be encouraged.

ii. The quality system requirement would depend on the intended country for export.

4.6.8 Location;

i. Location of the proposed factory without any risk of potential contamination from and/to the immediate environment and other manufacturing activities on the site will only be considered for approval.

4.6.9 Outsourcing of the services;

If outsourcing any type of the service related to manufacture (viz. quality control activities, research and development, processing stages, packing etc.) of the products is not scientifically or logically justifiable, the proposal will not be approved.

Grant of Provisional Authorization to set up the Manufacturing Plant

4.7 The Provisional Authorization to set up the manufacturing plant maybe granted when all the above conditions met and upon approval by the Bhutan Medicines Board.

4.8 The proponent will be briefed by the Authority on the overview of the regulatory system in Bhutan and conditions when issuing the Provisional Authorization and may involve undertakings from the client.

4.9 During the Provisional Authorization period, the facility is expected to be complete in compliance with the approved layout and fulfilling all the conditions issued during the approval.

4.10 The Provisional authorization is valid for 2 years and shall be renewed before expiry if the facility is not ready for operational.

4.11 A copy of Provisional authorization if renewed shall be submitted to Department of Industry, Ministry of Economic Affairs.

Facility Inspection and Approval for operational manufacturing

4.12 Once the premise or facility is ready for production, the applicant can request Authority for inspection of the facilities to observe and verify the premise if it is complying with approved plant layout and other aspects of Good Manufacturing Practices (GMP).

4.13 The proponent may request pre-authorization inspections when key stages in the technology transfer are completed or the application of Quality Risk Management regulatory expectations are completed.

4.14 The Authority shall inspect the facility for compliance with the approved plan, clear definition of the manufacturing processes and flow of the materials and personnel, adequate premises and space, suitable equipment and service, correct materials, containers, approved procedures and instruction and suitable storage as specified detail under the part II of this guideline.

4.15 There shall be validated system for treatment of water drawn from own or any other source to render it potable so as to produce Purified Water conforming to Pharmacopeial specification. Purified Water so produced shall only be used for all operations except washing and cleaning operations where potable water may be used.

4.16 Validation studies shall be an essential part of Good Manufacturing Practices and shall be conducted as per the pre-defined protocols. These shall include validation of processing, testing and cleaning procedures.

4.17 In case of the application considered deficient, the Authority shall provide the reasons in writing including the grounds for refusal and direction for improvements, if any.

4.18 In case of approval, the firm maybe advised to manufacture three consecutive batches in commercial scale (for pilot for 1:8) for process validation and stability studies for review by the Authority.

4.19 The first two batches shall be tested by third party quality control laboratory recognized by the Authority and cost of such test shall be borne by the manufacturer.

4.20 When all the above conditions are fulfilled, the proponent shall be advised to register their products with the Authority based on the

principle conditions outlined under section 11 of this document and detail requirements under "product registration guidelines".

4.21 The Provisional Authorization will be issued in a specified format.

Market Authorization/Product Registration

4.22 The products shall require market authorization from the Authority upon submission of the detail documents specified in the registration guidelines.

4.23 The registration will be provided in generics only if there is no registration of the patent from MoEA.

4.24 Good Manufacturing Practice Certificate (GMP) or equivalent quality system certification (medical devices) from the Authority shall be required for the purpose of registration.

4.25 Notwithstanding the above requirement, for those factories which have not received GMP certification/quality system certification and those which still have deficiencies will get product registration only after receiving testing report of the commercial batch from third party laboratory recognized by the Authority. But this approach shall be considered only for a period of maximum three (3) years.

4.26 For pharmaceuticals, application should be submitted separately for different strength, and dosage form and pack size of a same active pharmaceutical entity or a combination.

4.27 For pharmaceuticals, stability study report conducted at Zone IV (a) should be submitted as following:

i. Test reports of accelerated stability study conducted at 40 °C ± 2 °C/75% RH ± 5% RH covering a minimum time period of 6 months at the time of data submission.

ii. Test reports of long term stability study conducted at 30 °C ± 2 °C/65% RH ± 5% RH covering a minimum time period of 12 months at the time of data submission for new finished pharmaceutical products or a minimum of 6 months data for existing finished pharmaceutical products.

iii. When the long-term & accelerated data show little or no change over time and little or no variability, extrapolation of the retest period or shelf life beyond the period covered by long-term data can be proposed but the proposed retest period or shelf life can only be up to twice, but should not be more than 12 months beyond, the period covered by long-term data.

4.28 For finished pharmaceutical products, bio waiver shall be granted as per Annex 8, WHO Technical Report Series, No. 937, 2006 (current version will apply).

4.29 Notwithstanding the above sections on stability data requirement, site transfer of stability data if scientifically justified maybe accepted based on the international practices.

4.30 For new dosage forms, stability protocols should follow the guidance in the parent stability guideline in principle. However, a reduced stability database at submission time (e.g. 6 months accelerated and 6 months long term data from ongoing studies) may be acceptable in certain justified cases.

Post Authorization Changes, Renewal and Cancellation

4.31 In the event of non-completion of the construction of the facility within the valid period, the application may apply for the renewal of the Provisional Authorization.

4.32 The application must be made at least 30 days before the expiry date of Provisional Technical Authorization.

4.33 The application must be accompanied by renewal fee of Nu.500

4.34 A grace period of six months may be given with prescribed penalty after which the Provisional Authorization will be deemed cancelled or revoked from the actual expiry date.

4.35 Once cancelled or revoked, the application will be considered new application and same procedure for new will apply.

4.36 Renewal of Provisional Authorization maybe granted for twice with the prescribed renewal fees. However, for third time renewal, application maybe considered new if no appropriate justifications are provided to the Authority.

4.37 During the valid period of the Provisional Authorization, for any changes of the medicinal products in same therapeutic categories proposed for manufacture or approval in the changes on the layout of the premises, the applicant must submit the revised or additional documents depending on the degree of change proposed.

4.38 In lieu of the section above, if the changes proposed are major such as change of location, or a different type of formulation, or different therapeutic groups, or changes in facilities and equipment, or change in operation and process or such other changes as deemed major by the Authority, a new application shall be required. Such changes will also need to be informed to the DoI, MoEA.

4.39 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 or reject the proposed changes.

Stop Clock Principle and Turnaround Time

4.40 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.

4.41 A period of one (1) month is required for initial screening of the proposal, three (3) months for review of the technical layout of the plant and review by the Board.

5.0 Rejection, Suspension or Cancellation and Transfer of Technical Authorization

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

i. 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
ii. Any serious non-compliance reports have been received from GMP audit or any other external audits;
iii. Applicant defaults timely renewal beyond six months of grace period;
iv. The licensee obstructs the inspection of the manufacturing firms or premises; or
v. For any other matters as specified by the board at the time of cancellation.

5.3 Manufacturing Authorization will be automatically cancelled if the product marketing authorization could not be obtained for commercial purpose within three (3) years of issuance of it.

5.4 The Technical Authorization may be transferred to another individual or firm upon request by the licensee provided all the technical conditions remain valid.

5.5 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.

6.0 Certifications from the Authority

6.1 For the purpose of GxP certifications, in addition to the basic requirements for certification outlined in this document, the firm shall be eligible only after fulfillment of the conditions laid down in the GMP guidance document (separate document).

6.2 No certificates related to GxP shall be issued if the conditions of Good Manufacturing Practice (GMP) and licensing is not fulfilled based on the GMP inspection report of the Authority.

6.3 Manufacturers holding an authorization for wholesale distribution maybe issued with a Good Distribution Practice (GDP) certificate when a satisfactory inspection has been made in addition to GMP.

6.4 Good Laboratory Practices (GLP) maybe issued to manufacturing Quality Control Laboratories upon on the request of the manufacturer or

their clients.

6.5 Good Clinical Practices (GCP) maybe issued to Contract Research Organizations approved for the Clinical trials.

Certificate of good manufacturing practices (GMP)

6.6 GMP certificate or CoPP from the Authority will be issued only if there is no critical deficiency.

6.7 A 'critical deficiency' is a serious situation that requires immediate resolution and will result in regulatory action being considered, including suspension or cancellation of your GMP license or GMP clearance.

6.8 A deficiency can be critical when one of the following is observed:

i. Practice or process has produced, or may result in, a significant risk of producing a product that is harmful to the user;
ii. The manufacturer has engaged in fraud, misrepresentation or falsification of products or data.

6.9 Critical deficiency will be mentioned in the inspection report and may include the following deficiencies but are not limited to:

i. Absence, falsification or misrepresentation of manufacturing and packaging records
ii. Falsification or misrepresentation of analytical results or records
iii. No master batch documents
iv. No evidence that mandated recall processes have been complied with
v. Grossly unsuitable premises so that there is a significant risk of contamination
vi. Evidence of gross pest infestation
vii. Lack of sterilization validation
viii. Water system for sterile products not validated

6.10 In addition to the examples that apply to all manufacturers, here are some examples specific to the manufacture of medicines and APIs of Critical deficiencies include, but are not limited to;

i. Raw materials not tested (including proper identification testing) to ensure compliance with specifications
ii. Inadequate segregation of manufacturing of high risk products (such as penicillins, cephalosporins, cytostatics, steroids, hormones) resulting in a risk of contamination
iii. Release of materials or finished product for a registered medicine not meeting specifications

6.11 The company which does not have GMP certification/quality system or recertification will not be issued any new marketing authorization. Market Authorization of the registered products may be suspended or may not be renewed.

6.12 The manufacturer should apply for recertification within 6 months from their GMP certification or quality system certification expiration. If the applicant is not certified with GMP compliance within this period, the certificate will automatically cancelled and the company cannot claim WHO/GMP certification in their product, label, any form or format. The notification maybe published in DRA website.

6.13 If there is plan for outsourcing of laboratory activity, GLP certification is mandatory for GMP for the safety and reliability.

6.14 The validity of GMP certificate shall be one year unless otherwise revoked or cancelled.

Certificate of pharmaceutical products (CoPP) and free sale certificate

6.15 An industry shall receive certificate of pharmaceutical products from the Authority if it wishes to export drug products into the international commerce in the WHO prescribed format for CoPP.

6.16 Following document should be fulfilled to be eligible for acquiring CoPP from the Authority;

i. GMP certificate issued by the Authority
ii. A copy of Product marketing authorization certificate issued by Authority
iii. Process validation report of the concerned product(s)
iv. Updated Site Master File (SMF)

6.17 The validity of CoPP certificate shall be two years unless otherwise revoked or cancelled.

6.18 For Free Sale Certificate(FSC), following document should be fulfilled;

i. GMP certificate issued by the Authority
ii. CoPP certificate/a copy of Product marketing authorization certificate issued by Authority

6.19 The validity of FSC certificate shall be one year unless otherwise revoked or cancelled.

PART II
SPECIFIC REQUIREMENTS FOR THE MEDICAL PRODUCTS

7.0 Pharmaceuticals, Active Pharmaceutical ingredients and Traditional or Herbal medicinal products

7.1 Pharmaceuticals, Active Pharmaceutical Ingredients and Traditional or Herbal Medicinal products shall comply with the following specific requirements for Plant Layout in addition to the general plant layout requirements under Part I.

7.2 The Plant layout should indicate room sizes with intended activities in the various rooms such as sections of manufacture not limited to Production, Quality Control, stability study, control sample, microbiology, store (Raw Materials &Finished Goods), Quarantine, QA (documentation, validation and qualification etc.), Utilities (HVAC, water, ETP, maintenance, power supply, air compressor, equipment store, rest rooms, canteen recreation etc.).

7.3 The layout design should clearly depict the clean classification of different areas as per the qualification requirement. This should include pressure differential between the interfaces and provisions of appropriate air locks. Construction materials and finishing should be consistent with the area classification and qualification requirements. Type of products, intended manufacturing activities, appropriateness/type and size of the equipment should match with the room sizes.

7.4 Layout plan should be unidirectional with respect to flow of man, material and processes as per the concept of WHO GMP as shown in figure 2.

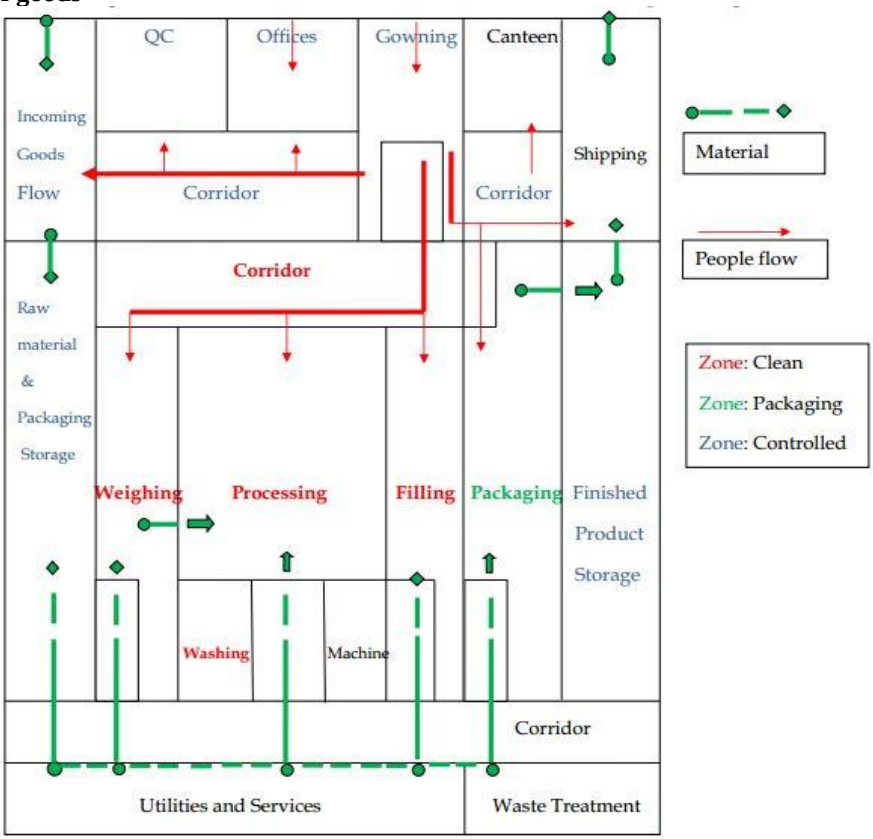

Figure 2 Example of material and people flow *(source: WHO GMP training module)*

7.5 Schematic drawings of the systems/Design Parameters of AHU/HVAC system applicable for different processing & non-processing areas within the manufacturing premises. The position of doors, PAL, MAL, pass boxes and change rooms, toilets/rest rooms

7.6 Schematic drawings of the purified/WFI water purification distribution loop design meeting pharmacopeial specification and qualification requirements.

7.7 Following basic facilities maybe required depending on the intended products for manufacture, not limited to the following:

	Intended Products for manufacture	**Facilities required**
i.	Hard/soft gelatin capsule	Facilities for Pulverizing, Screening, Mixing Drying, Gelatin blending, Soft gelatin processing, Soft capsule filling and pressing, Automatic or semi-automatic capsule filling and dust collection.
ii.	Pharmaceutical granules, tablets coated tablets, or pills	Facilities for Pulverizing, Screening, Mixing or annealing, Drying, Granulating, Milling, Tablet pressing or pill making, Gelatin or coating syrup blending, atomizing, coating, ventilation, drying, polishing facilities, Molding machines, buffing machines, and dust collection.
iii.	Pharmaceutical ointments (including eye ointments) or suppositories shall, as needed, install the following facilities:	Facilities for Powder grinding, Screening, Heating, Blending, Filling (packaging), Ointment tube sealing facilities where required, Suppository molding, Sterilization, air purification, aseptic filling (packaging) and sterility test and dust collection.
iv.	Injectables (including dialysates)	Facilities for the production of water for injectables, Ampoule cutting, Container drying, Sterilization, Cooling and storage, filling with precise measuring capabilities, Injectables container sealing, Sterilization, Injectables container seal and leak testing, Injectables foreign matter testing, distillation room, Changing room (for employees to change into sterilized work clothes, caps, face masks, gloves and shoes), drug solution preparation room, Drug solution filling and container sealing; Animal experiment area, facilities and equipment, equipped with necessary animals and breeding and observation areas;

		Area, facilities and equipment necessary for conducting plate count, sterility tests and other tests, Freeze-drying.
v.	Injectable antibiotics	For liquid form antibiotics, in addition to the requirement under the injectables, aseptic filling (packaging) facilities with appropriate temperature and humidity control capabilities, and automatic or semi-automatic precision scales, Doors/windows that open to the exterior shall be double doors/windows that seal tightly. Potency and safety testing facilities for antibiotic raw materials and products, Preparation rooms (for drying, sterilization and storage of packaging materials and containers, and other preparatory tasks related to packaging) and packaging rooms (with appropriate temperature and humidity control capabilities, and automatic or semi-automatic precision scales) installed in processing and packaging areas. Where antibiotics, hormones are produced, areas, facilities and equipment necessary for conducting bioassays shall be installed as needed.
vi.	Active Pharmaceutical Ingredients	Facilities for Isolation / filtration / drying / milling / sieving and packing operations; Ancillary area shall be provided for Boiler-house. Utility areas like heat exchangers, chilling workshop, store and supply of gases.
vii.	Traditional/Herbal medicines	Facilities for pulverizing, screening, drying, dust collection, re-packaging and packaging.

7.8 Testing Units shall include testing and instrument laboratories. Instrument laboratories shall be separate from testing laboratories, and shall be kept at an appropriate temperature and level of humidity and

air purity; testing laboratories shall be installed with sufficient and easy to use test benches, test stands, drug cabinets, fume hoods, water supply and washing facilities, as well as electric heating, thermostatic and drying facilities, and shall also be stocked with utensils and containers, chemical reagents and solutions, standard solutions and other necessary items.

Hazardous formulations and Active Pharmaceutical Ingredients

7.9 Applicant should consider the nature of product and probable risk prior to the approval and implementation of construction work.

7.10 Manufacturing facilities handling pharmaceutical products including active pharmaceutical ingredients (APIs) that contain hazardous substances such as certain hormones, steroids or cytotoxins, penicillin, cephalosporin and sex hormone should be designed in accordance with the main GMP principles to ensure quality of product, to protect the operators from possible harmful effects of products; and to protect the environment from contamination.

7.11 For manufacture of Penicillin, cephalosporins, a separate building facility at a distance not less than 50 meters from other factories manufacturing other category of medicines. It shall have independent Air Handling Unit (AHU)/HVAC system.

7.12 For steroid, sex hormone and oncology (cytotoxic) group and immunosuppressant groups, dedicated and self-contained facility shall be required. These self-contained facilities may be in the same building but should be separated by a physical barrier and have, e.g. separate entrances, staff facilities and air-handling systems. The extent of the separation from adjacent facilities and sharing of common services should be determined by risk assessment.

7.13 The link between the interior and exterior of the premises should be through airlocks (PAL and/or MAL), changing rooms, pass boxes, pass-through hatches, decontamination devices, etc. These entry and exit doors for materials and personnel should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time.

7.14 The changing rooms should have an arrangement with a step-over bench. The facilities on the exit side should incorporate showers for the operators.

7.15 The premises should be laid out and designed so as to facilitate the required pressure cascades and containment.

7.16 Plans should describe the ventilation systems, indicating inlets and outlets, in relation to other facility air inlet and outlet points.

7.17 The facility should be a well-sealed structure with no air leakage through ceilings, cracks or service areas.

7.18 Areas of the facility where exposed product presents a risk should be maintained at a negative air pressure relative to the environment.

7.19 The premises (and equipment) should be appropriately designed and installed to facilitate cleaning and decontamination.

7.20 The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) to ensure that the designation and conditions of use of all the rooms are correctly shown.

Active Pharmaceutical Ingredients (other than Hazardous API)

7.21 In addition to the general requirements, following conditions must be met for seeking Technical Authorization;

7.22 Air filtration systems including pre-filters and particulate matter retention air filters shall be used, where appropriate, for air supplies to production areas. If air is re- circulated to production areas, measures shall be taken to control re-circulation of floating dust particles from production. In areas where air contamination occurs during production, there shall be adequate exhaust system to control contaminants.

7.23 The final stage of preparation of a drug, like isolation / filtration / drying / milling / sieving and packing operations shall be provided with air filtration systems including pre-filters and finally with a 5 micron filter.

7.24 The requirements for the sterile active pharmaceutical ingredient shall be in line with the facilities required for formulation to be filled aseptically.

7.25 Sterile active pharmaceutical ingredient filled aseptically shall be treated as formulation from the stage wherever the process demands like crystallization, lyophilisation, filtration etc. All conditions applicable to formulations that are required to be filled aseptically shall apply same as for the manufacture of sterile active pharmaceutical ingredients involving stages like filtration, crystallization and lyophilisation.

Sterile Preparations, Parenteral Preparations (Small Volume Injectables and Large Volume Parenterals) and Sterile Ophthalmic Preparations

7.26 For sterile preparations, the various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are

divided into two categories; firstly those where the product is terminally sterilized, and secondly those which are conducted aseptically at some or all stages.

7.27 The various operations of component preparation (container's and closures), product preparation, filling and sterilization shall be carried out in separate areas within the clean area.

7.28 Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risks of particulate or microbial contamination of the product or materials being handled.

7.29 For manufacture of sterile medicinal products, PIC/S annex 1 "Manufacture of sterile medicinal products and WHO Technical Report series no. 961 (current version) shall be applicable for details requirements.

Veterinary medical products

7.30 For manufacture of Veterinary medicinal Products and Immunological veterinary medical products, PIC/S annex 4 and annex 5 shall be applicable.

Human Vaccines

7.31 For manufacture of human vaccines, WHO Expert Committee on Biological Standardization Sixty-sixth report, Annex 2 WHO good manufacturing practices for biological products shall be applicable.

Packing industry

7.32 For firm involved in packing the products originated from the domestic products will be authorized under following arrangements;

i. Infrastructure equivalent structure for premises/building with approved layout design (man, material, and process flow) from the Authority.
ii. The manufacturing activities should be undertaken and supervised by person with qualification, experience and expertise in related work.
iii. Adequate air handling units should be installed at least with 10 micron terminal filters supplying air to the units intended for external repacking.
iv. Quality control activities should be carried out in-house. If this is not feasible, products can be tested from authorized drug testing

laboratory as per formal agreement (contract analysis) between the company & the laboratory.

v. On the product label, the term "manufactured" will not permitted for the products which are not manufactured in the country.

vi. GMP certification maybe issued only for the limited scope of activities (packaging).

8.0 Medical devices (medical syringes and sterile disposable perfusion and blood collection sets and medical gases)

Medical devices shall comply with the following specific requirements for Plant Layout in addition to the general plant layout requirements under Part I.

8.1 For layout of the medical gases; premises used for the filling of medicinal gas cylinders should preferably be laid out in such a manner as to allow a flow through the area, with cylinder filling steps taking place in areas connected in a logical order corresponding to the sequence of the cylinder filling operations.

8.2 The licensee shall provide testing laboratory for carrying out Chemical and Physio-Chemical testing of medical devices and of raw materials used in its own premises.

8.3 Provided that the Authority shall permit the licensee in the initial stage to carry out testing of Sterility, Pyrogens, Toxicity on their products from the approved testing institutions but after one renewal period, the licensee shall provide testing facilities of all such tests in their own premises.

8.4 Following basic facilities are required depending on the intended products for manufacture, not limited to the following:

	Intended Products for manufacture	**Facilities required**
i.	Medical syringes	Moulding (wherever manufacture of medical devices is to start from granules), Facilities for gas processing, grinding processing, graduation mark facilities, syringe joint inspection, testing for glass alkalinity facilities, crack detecting, heat impact testing, standard volume testing, Airtight testing. Assembling (include cutting, washing and drying, sealing, packing, labeling, etc.) Storage Area, Washing, drying and sealing area (wherever required), Sterilization, Testing facilities.

ii.	Blood collection and blood transfusion devices (that incorporate plastic tubes)	Facilities for High-speed stirring, Stir cooling, Plastic pellet, High-pressure steam sterilization, High frequency welding, Water sterilization, and Aseptic operation rooms. Moulding (wherever manufacture of medical devices is to start from granules), Assembling (include cutting, washing and drying, sealing, packing, labeling, etc.) Storage Area, Washing, Drying and sealing area (wherever required), Sterilization, Testing facilities.
iii.	Hypodermic needles	Straight line facilities, facilities for grinding, needle valve seat, tightening, bend testing facilities, flexibility testing devices, Pull-out testing devices; pinch meters, microcalipers, micrometers.
iv.	Medicinal gases	Facilities for Storage, vaporizing, Air compression, purifying, filling. Space or facilities for empty cylinder storage area, empty cylinder sorting, quarantine area for filled cylinders, full cylinder storage area for released cylinders; and rejected area for Reject cylinder storage, Label storage, Quality control areas, Ancillary and Maintenance areas.

8.5 For Sterile disposable perfusion and blood collection sets, following equipment not limited to will be installed;

i. Moulding (Injection Machine, Extruder Machine and PVC Resin compounding Machine).
ii. Assembling (Hand Pressing Machine for filter fixing a Drip Chamber, Bag Sealing Machine, Compressor Machine, Leak Testing Bench, PVC Tube Cutting Machine, Tube Winding Machine (wherever necessary) and Welding Machine (wherever necessary).

8.6 For sterile disposable hypodermic syringes, following equipment not limited to will be installed;

i. Moulding (Granulator, Injection Moulding Machine, Weighing devices.
ii. Assembling (Blister Pack Machine, Vacuum Dust Cleaner, Rubber-tip Washing Machine, Foil stamping or screen printing equipment.

8.7 For sterile disposable hypodermic needles; following equipment not limited to will be installed;

i. Moulding(Needle grinding and leveling machine, Electro Polishing Machine, Cutting Machine, Injection Moulding Machine, Needle

Pointing Deburring Machine, Air-compressor.

ii. Assembling (Needle cleaning Machine with Magnetic Separator, Blister Packing Machine, Needle Inspection Unit)

8.8 Workbenches should be provided for carrying out operations such as moulding, assembling, labeling, packing etc. such benches shall be fitted with smooth impervious tops capable of being washed.

8.9 The premises should be kept under controlled conditions of temperature and humidity so as to prevent any deterioration in the properties of materials and products due to storage and process conditions.

8.10 The assembling area should be air-conditioned provided with HEPA filters. The moulding section shall, if necessary, have proper exhaust system.

8.11 The licensee should provide wherever required adequate equipment like water distillation still, deionizer, and washing machine. Dying Oven with trays for washing, drying and sealing of medical device.

8.12 The licensee should provide requisite equipments with required controls and recording device for sterilization of medical devices by Ethylene Oxide Gas in his own premises or may make arrangements with some Institution approved by the Licensing authority for sterilization. The products sterilized in this manner shall be monitored to assure acceptable levels of residual gas and its degradation products. An area of 10 square meters is recommended for basic installation of such facility.

9.0 Specific requirements for Medical gases

Medical gases shall comply with the following requirements in addition to all the general requirements under PART I and II;

i. Cylinders shall have storage areas clearly identified and provide suitable segregation to allow distinction between the various stages reached by given cylinders.

ii. Storage areas shall be kept clean, dry, well ventilated and free of combustible materials to ensure that cylinders remain in an appropriate condition compatible with the environment in which they will be used, up to the time of supply.

iii. In order to permit batch segregation, medicinal gas cylinder shall be stored in an orderly fashion with adequate segregation of different gases and of full/empty cylinders. The storage arrangements shall permit suitable rotation of stock to ensure that cylinders are used for supply to customers on a first in / first out basis.

iv. Segregated labelled areas shall be provided for the storage of complaint and reject cylinders.

v. Finished product analysis areas should preferably be separated from production areas, unless the analysis equipment is installed adjacent to the medicinal cylinder filling point.

vi. Cylinder labels and package inserts (patient information leaflets) are considered critical to the conformity of the medicinal gas product and special attention should be paid to the safe and secure storage of these materials.

vii. The layout of the medicinal gas quality control areas should have sufficient space for cylinder storage to avoid mix-ups or cross-contamination of sample cylinders. There should be adequate suitable storage space for all medicinal gas sample cylinders and for the associated records. A typical plant layout for medical gases is shown below in figure 3.

viii. Medicinal gases should preferably be filled in a separate area from non-medicinal gases. There should be no exchange of cylinders between campaign filling in the same area can be accepted provided that specific precautions are taken and necessary validation is done to ensure that there is no confusion between medicinal and non-medicinal gas cylinders.

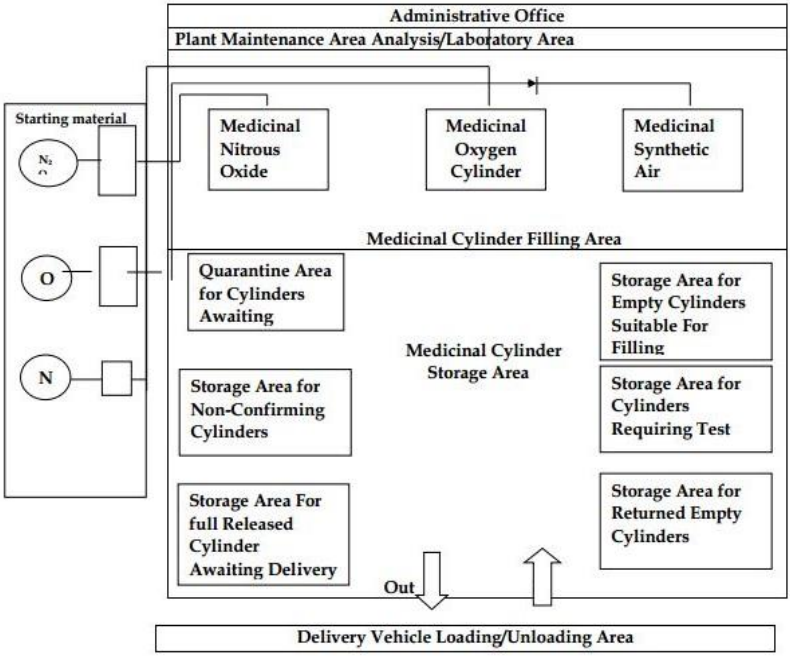

Figure 4: The layout of the medicinal gas quality control areas

ix. Clearly identification of the content of fixed distribution systems at their outlets and minimization of the “dead legs” where circulation may be restricted.

x. Identification of the pipelines carrying medical gases between areas by colour or by standard markings at suitable intervals and showing the direction of flow.

xi. Appropriate location of the air intakes used in the production of medical gas in a way that avoids contamination with waste gases and other pollutants. Filters—especially the ones used to trap desiccants after driers must be of suitable construction, and examined and changed as needed.

xii. Storage of filled cylinders/cryogenic vessels in a way that ensures they will be delivered in a clean state, compatible with the environment where they will be used.

xiii. Specification for the medicinal gas storage tanks for storage and distribution of refrigerated liquefied gases shall include:

a. Volumetric capacity / water capacity of the storage tank appropriate for the medicinal gas;
b. Design code, design pressure and the maximum working pressure of the storage tank;
c. Materials of construction;
d. Physical dimensions; and
e. Internal cleanliness requirements, the acceptance limits for both new and re-tested
f. Storage tanks statutory periodic inspection requirements.

For bulk production, it will only be acceptable to manufacture non-medicinal gases and medicinal gases concurrently, such as in an air separation unit, provided that the quality of the non-medicinal gas is at least equal to the quality of the medicinal gas.

xiv. Air filtration, In an Air Separation Unit, where atmospheric air is used as a raw material, it shall be filtered at the inlet point to restrict the intake of particulate matter into the plant.

xv. The medicinal gas cylinder filling manifolds shall be dedicated to the filling of either a single medicinal gas or to a given mixture of medicinal gases to different concentrations. The manifolds shall be equipped with filling hose connectors that correspond only to the valve outlet for that particular gas or mixture of gases so that only the correct containers can be attached to the manifold without the use of an adapter.

xvi. The name of the gas or gas mixture being filled shall be displayed on each medicinal gas cylinder-filling manifold. An exception to this rule is described in the "shared filling system.

xvii. Medicinal Cylinders should be labelled and painted correctly, according to the national standards and to comply with the relevant marketing uthorization;

Gas	**Colour of cylinder**
Oxygen	White
Nitrous oxide	Light blue
Nitrogen	Black
Medical air	Black and white

xviii. Filling of medicinal gas cylinders shall be avoided in non-medicinal gas cylinders filling areas and not filled with equipment used for filling non-medicinal gas cylinders. Filling lines used to supply medicinal gas filling areas should be dedicated to that service.

xix. In exceptional circumstances, where it is impracticable to have a dedicated medicinal gas cylinder filling facility, the principle of campaign filling may be used to allow medicinal gas cylinders to be filled on non-medicinal gas cylinder filling equipment.

xx. In these circumstances, the area shall be dedicated to medicinal gas cylinder filling during the campaign and appropriate tests and procedures carried out to ensure that the product is not contaminated with non-medicinal gas and the cylinders filled comply with the relevant specifications.

xxi. Where an automated filling process is not available for the filling of medicinal gas mixtures, there shall be a documented procedure to demonstrate that the mixtures have been filled correctly and consistently and that there has been no backflow from any other cylinder filling process.

xxii. Storage tanks and mobile delivery tankers shall be dedicated to one gas. The quality of the gas stored in the storage tank or mobile delivery tanker shall be well defined and shall be at least equal to the medicinal gas quality standard.

xxiii. Bulk medicinal gases from the manufacturing plant may be stored in the same batch or bulk storage tank as non-medicinal gases, provided that, the quality of the non-medicinal gas is at least equal to the quality of the medicinal gases.

Market authorization for medical gases

9.1 There shall be appropriately authorized and dated specifications for all starting materials, including bulk products, packaging materials and finished medicinal gases.

9.2 Starting and packaging materials; Specifications for starting materials and packaging materials used for the production of medicinal gases or the filling of medicinal gas cylinders shall include, as appropriate:

i. Description of all of the starting and packaging materials;
ii. Chemical formula of the starting material;
iii. Designated name or reference code of the starting material;
iv. Relevant pharmacopoeia monograph of the starting material, where specified;
v. Original producer and the approved suppliers of the materials;
vi. Specimen of the product label;
vii. Detailed methods for the sampling and testing of the starting materials, including any
viii. Specified analytical procedures and equipment;
ix. Qualitative and quantitative testing requirements of the starting materials with the
x. Acceptance limits; and Storage conditions and precautions.

9.3 Specifications for bulk medicinal gases shall be available where they are purchased for the production of finished products, dispatched for supply to the customers; and referred to for the evaluation of the finished product.

9.4 The specifications for the bulk medicinal gases shall include, as appropriate:

i. Chemical formula;
ii. Designated name or reference code;
iii. Description of the pharmaceutical form of the bulk medicinal gas;
iv. Detailed methods of sampling and testing the bulk medicinal gas, including the specified
v. analytical procedures and equipment;
vi. Qualitative and quantitative testing requirements for the bulk medicinal gas, with acceptance limits;
vii. Storage conditions and any handling precautions; and
viii. Maximum period of storage before re-examination.

9.5 Specifications for finished medicinal gas shall include:

i. Designated name of the product;
ii. Relevant pharmacopoeia monograph, where specified;
iii. Chemical formula and the concentration of each component, where appropriate;

iv. Description of the pharmaceutical form of the finished product;
v. Relevant details of the gas cylinder, cryogenic container and the outlet valve;
vi. Detailed methods for the sampling and testing of the finished product, including the specified analytical procedures and equipment;
vii. Qualitative and quantitative requirements for the finished product, including the acceptance limits;
viii. Specimen of the product label and patient information leaflet where appropriate;
ix. Storage conditions and any handling precautions; and
x. Shelf life of the finished product (where detailed in the relevant marketing authorization).

9.6 Specifications for medicinal gas cylinders used for storage and distribution of compressed or liquefied gases or refrigerated liquefied gases shall include:

i. Water capacity of the cylinder and the volumetric content for the appropriate medicinal gas;
ii. Design code, design pressure and maximum working pressure of the cylinder;
iii. Material of construction of the cylinder;
iv. Colour coding for its intended gas service;
v. Physical dimensions of the cylinder, where required;
vi. Any internal cleanliness requirements, including the method of cleaning and the acceptance limits for both new and re-tested cylinders;
vii. Statutory periodic inspection requirements; and
viii. Approved suppliers and retesting facilities (if any).

9.7 Specifications for cylinder valves fitted to medicinal gas cylinders for storage and distribution of compressed, liquefied or refrigerated liquefied medicinal gases shall include:

i. Materials of construction - of the cylinder valve, with specific reference to the compatibility
ii. of materials used in its manufacture with the medicinal gas for its intended service;
iii. Design pressure and maximum working pressure of the cylinder valve;
iv. Testing criteria and any maintenance requirements for approving the valve for use;
v. Inlet and outlet connections (as appropriate) with reference to the appropriate valve outlet

vi. Standards (national or international standards);
vii. Approved method of operation; and
viii. Approved suppliers and retesting facilities, where appropriate.

9.8 Specification for printed cylinder labels and patient information leaflets shall include:

i. Label and leaflet material including details of the inks, adhesives and any protective
ii. Coatings, where appropriate;
iii. Printed text details (including the version control reference). A specimen of the current version of the printed materials shall be retained with the specification; and
iv. Approved suppliers (if any).

References:

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

i. The Medicines Act of the Kingdom of Bhutan 2003
ii. National Drug Policy 2007
iii. Bhutan Medicines Rules and Regulation 2012
iv. PIC/s guideline document Part 1 and 2
v. World Health Organization, Technical Report Series, 961
vi. World Health Organization, Technical Report Series, No. 953, 2009
vii. Medicines Registration Guidance, Government of Nepal Ministry of Health Department of Drug Administration, Nepal 2016
viii. Good manufacturing Practices for drug products, Health Canada
ix. Schedule M, Good manufacturing practices and requirements of premises, plant and equipment for pharmaceutical products
x. Good manufacturing practice guide for medicinal gases AIGA 023/17(Revision of AIGA 023/05) Asia Industrial Gases Association accessed on 12 October 2018 http://www.asiaiga.org
xi. Taiwan Food and Drug Administration, accessed on 15 October 2018www.fda.gov.tw

Annexure-1 Format for Proposal

i. Front Page (Title, Physical address, Postal address, Telephone number and fax number, if available and Email address)
ii. Introduction of the project (What the project is all about), scope of activities (What type of medical products, mention intended products), installation capacity, project cost etc.
iii. Objectives of the project (Purpose)
iv. Source of raw materials (Mention name of countries of raw material are to be imported)
v. Target Market (mention the countries where the products are likely to be exported)
vi. Promoters details (Name and addresses); in case of FDI, details of foreign investor/partner.
vii. Technology collaboration if any (mandatory in case of FDI):
viii. Proposed site detail:
Bird's eye view or Sketch map/Pictorial presentation,
Size of the proposed site,
Location:
Immediate environment and other manufacturing activities on the site, if available):
(*he layout design of the proposed manufacturing area should be appended with site plot, covered/uncovered land area ratio, activities being conducted in adjoining areas and environmental aspects).*
vii. Technical Aspects:
Brief description of the Quality Management System:
Arrangement on production and quality control activities:
Mention any services to be outsourced (if any):
Engineering and maintenance Services:
Project Management:
Type of products intended for manufacture with therapeutic categories:
List of intended manufacturing equipment to be procured:
Intended size of the employees:
viii. Waste Management Plan: *(It should include detailed plan for management of wastes generated from the manufacturing plant).*

Drug Regulatory Authority

Promoting availability of quality, safe and efficacious medicinal products for consumers

Drug Regulatory Authority

Royal Government of Bhutan

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