**Standard Operating Procedure: HM Pharmaceutical & Medical Supplies**

**Short Description of the company**

HM Pharmaceutical and Medical Supplies with its head office at the NPPF Colony, in Phuentsholing, Bhutan deals with the supply of drugs, equipment, vaccines, and medical consumables to various stakeholders, the Ministry of Health being the most important stakeholder.

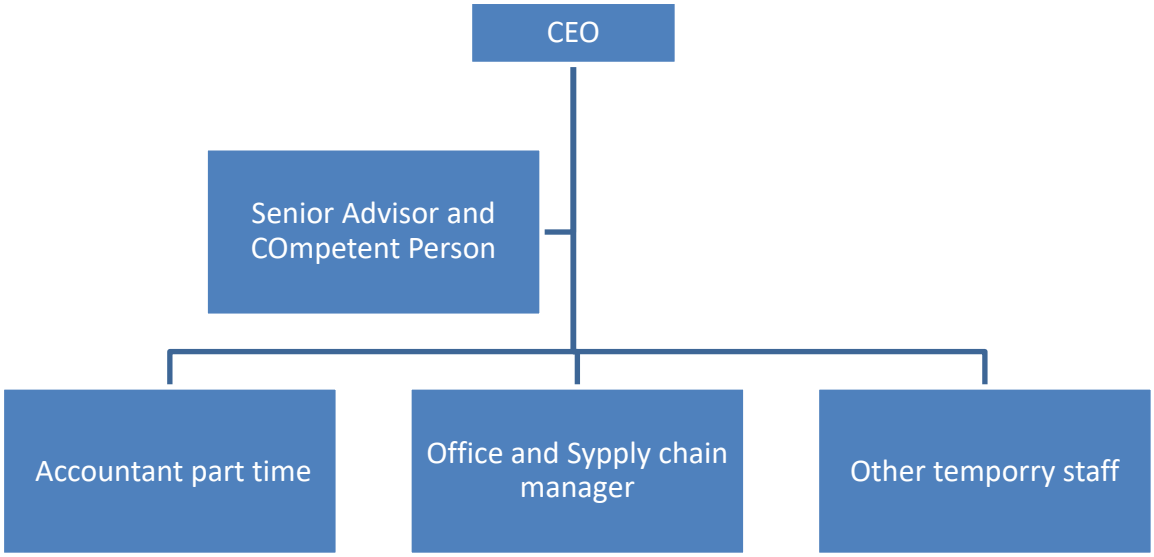
We are registered with the Drug Regulatory Authority of Bhutan under registration No. DRA/TA/2020/185. Our competent person is registered under registration No. DRA/REG/CP/2020/707. We are registered with the Ministry of Ministry of Industry and Commerce under license No.W2003373 and with the Department of Revenue & Customs under the Business Income Tax No. HA.B11766. Date of Rgistration: Initially as HM Enterprise on 4th Jan 2017 and changed to HMPAMS 8th Dec. 2020

Following are some activities conducted within the GxP context:

1. We liaise with genuine medical and equipment manufacturers that have GMP certification or have WHO approved products;
2. We work with manufacturers with products registered in PIC countries;
3. We endeavor towards getting drug/ products registered that are prequalified by WHO,UN,OIE or other UN recognized international organizations;
4. We ensure right physical environment recommended by the manufacturer for those products we supply supplied to our buyer;
5. We follow rules and regulations meticulously, set by the BDRA, Royal Government of Bhutan.

The organization is headed by a CEO. The senior advisor to the company is also the competent person who looks after business development and regulatory measures. A supply chain manager who also looks after office administration and maintains day to day office expenditures runs the office. We hire accountant periodically to maintain accounts and finance of the company. Apart from that we hire other personals to support the office as and when required.

**Organogram**




**Business continuity plan**

We do not have a separate Business Continuity Plan for GxP activities within the organization. However we follow the following to ensure we continue GxP activities.

1. We continue to keep ourselves abreast of Bhutan Medicines rules and regulations.
2. We learn of any regulation changes.
3. We liaise with manufacturers with cGMP certification only.
4. We strive to get drugs registered in PIC countries, or those that are approved by WHO, UN etc.
5. We follow all GxP advise given to us by principle manufacturers while handling their products.

**Process for Data Protection**

Important manufacturer information are handled by one to two persons only.viz. CEO and Senior Advisor and Competent Person. The computers of these persons are passport protected. It is the company's policy that Information's from manufacturers are not shared with anyone unless the manufacturers desire so. In case of need of dissemination of company Information Company's clearance with a written permission to share such documents must be made available. In case of leakage or evidence of pilferage of data, the Information officer who is also

the CEO of the company will be immediately informed for immediate enquiry, investigation and further prevention of loss/pilferage of information.

**Cold chain management**

All vaccines and insulin is provided by the Royal Government to all health facilities. So far, insulin is not sold in the open market, nor is vaccine sold to clients directly. Hence, there has been no need for us to maintain cold chain equipment. However, we have the capacity and can increase it to fulfill the requirements of cold chain management.

The BFDA has set guidelines for management of products that need cold chain facility. Record of temperature profile need to be maintained twice every day. These are paper based and the BFDA inspectors visit the center without informing the vendors to check cold chain maintenance. Records are paper based. However, this can be upgraded to electronic records too.

**Sample management procedure**

When free samples are received, we enter the samples with relevant information in our sample register. Proper environment is maintained to ensure samples are stored properly. We distribute the samples to the end users at the earliest and record its distribution. We provide feedback to the principle company of the distribution. Any remaining and date expired samples are disposed through approval of BFDA. We follow the above procedure for sample use.

**Internal Audit program**

We don't have an internal audit program as yet for GxP activities. We do not manufacture but supply pharmaceutical products. To ensure that pharmaceutical products we supply are safe and meet the intended use, we adhere to picking up companies with cGMP certifications, products approved by WHO, UN or other international organizations etc. We also follow strict product registration procedure.

**Regulations**

We are bound by Medicine Act of Kingdom of Bhutan 2002. This act provides the constitution of a composite Council for regulation of the medical and Health profession in all its aspects especially in respect to ethics and matter connected with health. Furthermore, Bhutan Medicines Rules and regulations came in to being in 2008 which was revised in 2019. The B FDA of Bhutan informs all competent persons of any change in the rules and regulations which the competent persons need to know all the time. We are guided by the act and follow regulations as in the rules and regulations documents. As and when new regulations are formulated, the BFDA notifies all the companies involved in manufacture and import of medicines and medical devices of such regulatory changes through mail. Furthermore, the BFDA conducts workshops and informs and explains such changes as and when needed. There is no set procedure for receiving such regulatory changes.

**Confidentiality**

Information of a customer is kept confidentially under lock and key and password protected. Sensitive informations are handled by limited number of responsible persons. Such informations are not made public. Informations are not shared to other customers. Confidential informations are shared only when required by the law of the land. We have agreement on confidentiality of documents/facts and figures with principal company (customer) which we follow strictly.

**Dossier submission process**

1. Decide on the product to be registered with B FDA with the principal company.
2. Share the Royal Government Product registration guideline with regulatory team of the principle company.
3. Discuss with the regulatory team of the company on issues for clarity.
4. The Regulatory team prepare dossier as per the guideline of the BFDA.
5. ACTD format is followed for dossier preparation.
6. The regulatory team of the company share the dossier with HMPAMS.
7. We review the dossier, analyze gaps and inform the principle company if any.
8. Regulatory team of principle company review query and include information required thereof.
9. We evaluate and approve art work and labels prepared for Bhutan by the principle company.
10. 8. We receive samples required for registration.
11. We conform all information included in the dossier through a checklist we have prepared, are ,made available in the dossier.
12. We submit the dossier online to the BFDA.
13. After the preliminary screening, and BFDAs conformation, we submit required samples and initial submission fees.

**Ensuring quality of dossier**

1. We ensure that documents in the dossiers are as per the checklist prepared by us which is in accordance with the BFDA guideline for product registration.
2. We ensure each document in the dossier as per the guideline.
3. We review every document in the dossier viz. Part 1 Administrative documents 2. Technical documents, ensuring correct information is provided and those documents requiring notarization is done.
4. We follow ACTD format of dossier preparation.
5. We evaluate and approve the art work submitted to us for approval.
6. After we review the documents thoroughly, our team approves the dossier for submission.
7. We submit the dossier online for receipt and review by the BFDA.

**Tracking of Dossier after submission**

The BFDA upon receipt of the dossier takes a weeks' time to have a preliminary assessment of the dossier to ensure its completeness after which we are asked to submit samples and pay initial submission fees. Following that, the BFDA takes time to go through the dossier within the next four weeks. Query are sent to us which we reply or seek clarfication from the principle company of such query. If all documents are furnished correctly, BFDA registers the product in 8 weeks time of submission. Every step is informed to us by the BFDA. We follow up with BFDA after the initial submission of dossiers to complete missing documents (queries) once every month. Dossiers submitted as well as all queries answered and any other additional document furnished are all kept/achieved electronically with us in our office in separate folder for each product as back up (database). We have two computers and a backup drive where data base is kept. Only two individuals have access to these data.

**Matrices to assess quality of deliverables.**

We have submitted 10 to 15 dossiers each year to the BDRA for the last 4 years. We work only in Bhutan. We do ensure the following for quality of deliverables:

1. Accuracy: We ensure that the deliverables are free from factual errors, inaccuracies, or misleading information.
2. Completeness: We verify that the deliverable includes all the necessary components, elements, or features as specified in the requirements.
3. Timeliness: We try ensuring deliverable are delivered within the agreed-upon timeframe.
4. Adherence to Requirements: Evaluate and adhere that the deliverable meet all specified requirements, standards, and specifications outlined.
5. Clarity and Readability: We ensure that the deliverables are presented in a clear, understandable, and organized manner.
6. Consistency: We check for consistency in language, tone, style, and branding across different sections or components of the deliverable.
7. Compliance and Legal Considerations: We ensure that the deliverable complies with relevant laws, regulations etc.
8. Customer Satisfaction and Feedback: Our motto is customer satisfaction.

**Types of dossier submission:**

1. New Drug Applications (NDAs): These are submitted to seek approval for registration of a new pharmaceutical product.
2. Generic Drug Applications (GDAs): Submitted for generic versions of existing approved drugs.

3. Biologics License Applications (BLAs): These are for biopharmaceutical products, such as vaccines.
4. Variation Submissions: These involve changes to the existing product, such as modifications to the manufacturing process, labeling, or formulation.
5. Transfer of Marketing Authorization: When a company wants to transfer the authorization to market a drug to another entity.
6. Orphan Drug Designation Applications: These are for drugs intended to treat rare diseases.
7. Device registration.

**Dossier management guideline**

Following are some steps and measures for dossier maintenance:

1. Have paper based dossier as well as electronic dossiers.
2. Structured system
    a. Paper based dossiers: labeled and organized folders
    b. For digital dossier: Folders are created with names
3. Categorize and label: Organize as GDA. NDA, Biologicals and Device or as per the manufacturers requirement
4. Regular review of dossiers ensuring renewal are initiated well on time.
5. Backup: For digital dossiers, back up is created to prevent data loss.
6. Access control: The dossiers as well as the registration certificates are kept in password protected folders or under lock and key for paper based certificates for security.

Dossiers are archived till the product is deregistered with the BFDA either by the principle company (as per company regulations) or we deregister after 3 years the product are not in Bhutan . However, if the principle company wishes that the product is kept registered, we renew the registration every three years.

**Management of regulatory variation**

Managing regulatory variations involves ensuring that a collection of documents or information complies with the various regulations, standards, or requirements that may apply to the subject matter.

1. Identify Applicable Regulations: Identifying specific regulations, standards, or requirements that are relevant to the dossier;
2. Regularly Monitor Changes: Regulations can change over time. The BFDA notifies of any regulatory changes. Keep a close eye on such notifications;
3. Create a Compliance Checklist which will serve as a reference to ensure that the dossier is compliant with all relevant regulations;

4. Regular Reviews: Conduct regular internal reviews and audits to check for compliance with all regulations;
5. Address any non-compliance issues promptly;
6. Engage with Regulatory Authorities: In cases of ambiguity or uncertainty regarding regulatory compliance and variations, consider reaching out to the relevant regulatory authorities for clarification or guidance;
7. Adapt to Changes: Make necessary adjustments to the dossier as regulations evolve or new requirements are introduced;
8. 8. We have moved to ACTD format of dossier preparation from previous conventional indigenous format to which we have successfully transitioned since 2022.

**Named patient drugs (unregistered drugs import procedure): drugs unregistered like named patient drug, orphan drug, drugs for epidemic containment, research purpose;**

1. Get the medicine filled up in form 2 (a special form) and signed by concerned specialist.
2. Get the drug dosage and duration verified by the hospital pharmacist.
3. Apply online to the BFDA for import authorization of unregistered drug in prescribed form.
4. BFDA verifies and provides authorization for import of such drug.
5. Purchase is made and import authorization of the drug is made.

Other situations when unregistered drugs are imported are for special drugs recommended to contain epidemics, orphan drugs, drugs that are unregistered but are essential (EDL).

**Variation in labels**

The Authority must be notified of any changes to the product's label before the product is imported. HMPAMS apply for post approval variations during the valid period of registration. Following are some data requirement for post approval variation for products label change:

1. Official letter from principle manufacturer requesting for the change of product label.
2. Submit proposed product label, a clean and annotated version highlighting the changes.
3. Letter of declaration from the manufacturer and MAH stating that no other changes on the label except for the intended change.
4. Label change is applied to the BDRA in the prescribed form.
5. BDRA goes over the request, and approves the new label.

**Maintaining records on labeling changes**

Collecting and maintaining data and records related to labeling changes is crucial for regulatory compliance, quality control, and product safety.

1. Document Identification: Assign unique ID numbers to each document or label to track changes.

1. Data repository: Create secure digital repository for storing all labeling-related data and records. This is cloud-based storage system;
2. Documentation: Clearly label each version of label and record the changes made.
3. Regulatory Guidance: Stay informed about regulatory requirements and guidance related to labeling, as these may change over time.
4. Regulatory checks and references: Maintain copies of all regulatory submissions related to labeling changes, as these are crucial for demonstrating compliance.

**Quality control on labeling implementation**

Record of labels are kept in electronic files as approved in the registration process. During the time of supply of the said product the principal company must supply products with the same labels. However, if there has been a change in the label with the principal company, HMPAMS must apply for label variation with the BFDA for approval before import of such product.

**Communication with patients and health care professionals**

Our primary responsibility is to ensure that the information we provide to patients and healthcare professionals is accurate, clear, and compliant with regulatory requirements.

1. Identify required materials: These materials should contain essential information about the drug, its usage, potential side effects, and any special instructions;
2. Regulatory compliance: Ensure that all informational materials comply with regulatory requirements in Bhutan where the drugs are distributed;
3. Clearly and accurately present information on the drug's label and package insert. Include dosage instructions, contraindications, warnings, precautions, adverse reactions, and other critical information. Ensure that the font size and format meet regulatory standards for readability;
4. Consult Health Professionals: Offer consultation services to healthcare professionals who may have questions about products. Ensure accurate and timely responses to queries are made;
5. Provide educational resources for healthcare professionals, such as product monographs, prescribing information, clinical studies, and safety data. These resources can help them make informed decisions about products. These are materials developed by the principle manufacturer;
6. Online resources: Provide available online resources to the prescribers;
7. Drug safety information: Communicate information related to drug safety, recalls, or post-market surveillance to healthcare professionals promptly;
8. Pharmacovigilence: Encourage healthcare professionals and patients to report adverse events associated with products;

Effective communication is crucial for patient safety and healthcare professional decision-making. We are committed to provide accurate and comprehensive information that can

contribute to positive patient outcomes and trust in your products. Our primary client is the ROyal GOvernment hospitals. Each pharmacy unit in major has pharmacovigilence section who recieve adverse event report from end users.Pharmacist of smaller hospitals also are responsible for pharmacovigilence.  It is the role of pharmacists in hospitals to explain about drug side effects and possibility of adverse eventts which clients report to them in case they develop so. They also receieve and convey to higher hospital pharmacovigilence unit about any untoward issues related to drugs and vaccines.

**Promotional materials and regulatory compliance**

Promotional materials for pharmaceutical products must comply with local laws, regulations and industry commitments and it is critical to maintaining integrity of pharmaceutical industry and ensuring patient safety. Following are some steps that are followed:

1. Knowing rules and regulations pertaining to drugs and its promotions is essential.
2. Reviewing the promotional materials provided by the principal company or are developed locally adhere to local rules and regulations.
3. Ensure labels and inserts are all as approved by the BFDA during the process of product registration.
4. Approve the promotional materials within the company following its review.
5. BFDA clearance: Promotional materials are submitted to the BFDA for approval for public dissemination.
6. Monitor promotional activities and identify and rectify non-compliant materials and practices.
7. Ensure promotional materials developed for patients and health care workers are accurate and not misleading.
8. Mantain record of all promotional materials disseminated and a copy of each for future reference.
9. Seek legal consultation whenever necessary.

**Review of promotional material**

**1.** Promotional materials are reviewed to ensure it complies with regulatory requirements, are accurate, aligns with company's policies, and are need based.
   1. Establish a review team;
   2. The review team to understand regulatory requirements;
   3. Define goals and objectives of promotional materials review;
   4. The review SOP to include steps, tools etc.;
   5. Initiate review to assess materials content, message, accuracy, alignment with local regulatory requirements and alignment with  goals and objectives of the principle company;

6. Ensure promotional materials are accurate, scientific, regulatory requirements are fulfilled, are clear and consistent, facts are accurate;
7. Assess any risks with the promotional materials;
8. Get feed back from all team members and other relevant members of the office;
9. Perform a final review;
10. Make document revisions and changes of promotional materials as suggested;
11. As the materials passes through the review process successfully, it is then approved for mass print and dissemination;

Competent person is responsible for the above process along with support from other members of the organization.

**Promotional material inventory**

Record of all promotional material received is kept. An inventory is developed to track available and distributed promotional materials. Every time promotional material is distributed, it is updated in the stock register to ensure a record of where have such materials moved to and what is the stock in balance.

**Process of destruction of withdrawn and old promotional materials**

The process of ensuring proper destruction of promotional materials after withdrawal is essential for maintaining compliance with regulatory requirements and preventing unauthorized use.

1. Initiate a formal notification process to inform all relevant stakeholders of the withdrawal.
2. Establish a centralized location, whether physical or digital, where all copies of the withdrawn promotional materials are collected.
3. Store the withdrawn materials securely until the destruction process take place.
4. Create inventory of all withdrawn materials, specifying quantities, versions, and any relevant identification details.
5. Determine a specific timeline for the destruction of the withdrawn materials.
6. Assign responsible team to oversee and varify destruction process.
7. Select appropriate methods for destruction. Options include shredding, incineration, or secure disposal. For digital files, ensure that they are securely deleted and made unrecoverable.
8. Document Destruction Process and report to the principal company and other relevant authorities including stakeholders and BDRA.
9. Obtain certificates of destruction from the service providers or individuals responsible for carrying out the destruction.
10. Maintain records of the withdrawal and destruction process in accordance with regulatory requirements.

**Translation of promotional materials and regulatory requirements**

English is our official language in Bhutan and all health care workers are proficient in English. Most materials are received in English language. We also ask the principal company to share documents in English. Hence, there is no need of translation of documents or other materials. On the issue of translating posters and materials for patient's consumption, we outsource the material for translation to the local media house that has translators with local regulatory expertise. Our team reviews such materials for its appropriateness to the local context. Our translation needs are very less.

We do not have translators with health regulatory expertise. However, these translators are conversant with general rules and regulations of the country. We provide posters in very simple english for translation to local language. Our team reviews the translated posters to ensure that these are within the regulatory norms of Bhutan.

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