GOOD DISTRIBUTION PRACTICES FOR PHARMACEUTICAL AND BIOLOGICAL DRUG PRODUCTS

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1. HISTORY

This is the first edition of Guidelines on Good Distribution Practices (GDP) for Pharmaceutical and Biological Product.

2. APPLICATION-Guidance for Industry

This document is applicable on the pharmaceutical and biological drugs' manufacturers, importers, exporters, suppliers, distributors, wholesalers, and related entities involved in the supply chain of pharmaceutical and biological products.

This document will also serve as a guide for developing SOPs of GDP for implementation, as well as for public and private healthcare institutions, donor agencies, and healthcare workers involved in the procurement, trade, and distribution of pharmaceutical and biological products.

3. PURPOSE

These guidelines are intended to ensure the integrity and quality of pharmaceutical and biological products during all aspects of distribution and supply chain. In order to maintain the quality of pharmaceutical and biological products, every activity in the distribution should be carried out according to the principles of Good Storage Practice (GSP) and Good Distribution Practice (GDP).

This document outlines the principles for the safe storage and distribution of pharmaceutical and biological products, emphasizing the importance of compliance to Good Distribution Practices by all parties involved, which greatly outlines best practices for their roles and responsibilities, from the manufacturer to the person dispensing or providing pharmaceutical and biological products to the patient or consumer.

These recommendations provided in these guidelines are in addition to the national and provincial drug laws (DRAP Act 2012, Drug Act 1976 and rules frame there under) as applicable on the manufacturers, importers, distributors, wholesalers and other relevant entities involved in the supply chain of drug products. These guidelines are not purported to be an interpretation of law and is for guidance purposes only.

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4. INTRODUCTION

Distribution of pharmaceutical and biological products is an important activity in the integrated supply-chain management of these products. In current world, supply chain and distribution system of drug products is increasingly complex as it involves various entities which are generally responsible for the handling, storage, and distribution of such products. These guidelines provide appropriate systems and structure to assist distributors and wholesalers in planning and conducting their activities, which will be helpful in prevention of proliferation of unauthorized/unregistered, substandard and falsified products in the market.

This guidance document sets out appropriate steps to assist in fulfilling the responsibilities involved in the different aspects of the distribution process, and intended to apply to all steps in the distribution/supply chain. The relevant sections should be considered by various role players as applicable to their role in the distribution process. Compliance with these guidelines will ensure control of the distribution chain and consequently maintain the quality and the integrity of supply chain system.

Distribution of drug products includes all activities consisting of procuring, holding, supplying, importing, or exporting of products. Such activities are carried out by the marketing authorization /registration holder including manufacturers/importers or their authorized distributors and NGOs, which supply products to the pharmacies/licensed drug sale outlets and healthcare institutions which are entitled to dispense drug products to the public.

Weak points in the distribution processes of drug products provide an avenue for substandard and falsified (SF) products to enter the supply chain. This is a concern in both developed and developing countries. DRAP in collaboration with the Drug Control Organizations of all federating units including Provincial governments, States and Territories intended to develop a joint approach to maintain an integrated supply chain system to ensure provision of safe, quality, and efficacious drug products to the public, and eradicate substandard and falsified products through blockage of their entry into the supply chain system.

5. LEGAL BACKGROUND

Under section 7c(ix) of the Drug Regulatory Authority of Pakistan Act 2012, DRAP is empowered to implement internationally recognized standards such as Good Laboratory Practices (GLP),current Good Manufacturing Practices cGMP, Good Distribution Practices (GDP), cold chain management, bioequivalence studies, stability studies, anti-spurious codes, clinical trials, bio-similar evaluations, and endorsement and systematic implementation of World Health Organization, International Conference on Harmonization and Food and Drug Administration guidelines etc.

Under section 7(f) of DRAP Act 2012, DRAP is empowered to coordinate at policy level and provide policy guidance to the Provincial Government in the performance of their functions with a purpose to bring uniformity.

Under section 7(t) of DRAP Act 2012, DRAP is empowered to develop issue, adopt, and enforce the standards and guidelines to ensure safety, efficacy, and quality of therapeutic goods with rational use at reasonable price.

6. DEFINITIONS AND ACRONYMS

Agreement	Arrangement undertaken by and legally binding on parties.
Authorized Officer	Officer appointed and entrusted to issue import clearance certificate under section 9 of Drug Import export rule
Batch	A quantity of any pharmaceutical product produced during a given cycle of manufacture;
Batch Number	A distinctive combination of numbers and/or letters which uniquely identifies a batch, for example, on the labels, its batch records and corresponding certificates of analysis
Change Control	The processes and procedures to manage system changes.
Clearance Certificate	A certificate issued on invoice of imported material before release of consignment form customs
DML	Drug Manufacturing License
DRAP	Drug Regulatory Authority of Pakistan
DSL	Drug Sale License
E-Commerce	Electronic /online Commerce
Falsified Product	Falsified product contains both spurious and counterfeit terms. A factitious pharmaceutical product which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products, and counterfeit pharmaceutical products may include products with the correct ingredients, with the wrong ingredients, without active

	ingredients, with an incorrect quantity of active ingredient or with fake packaging
FEFO	First Expire First Out
GDP	Good Distribution Practices; is that part of quality assurance which ensures that the quality of drug products is maintained throughout all stages of the supply chain from the site of manufacturer to the pharmacy or person authorized or entitled to supply drug products to the public.
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GPS	Global Positioning system
GSP	Good storage Practices
HVAC	Humidity Ventilation Air conditioning
ISO	International Standard Organization
L.C	Letter of credit
MA	Marketing Authorization is the registration of that drug product by the Registration Board of DRAP
NGO	Non-Governmental organization
Qualified Person	Legally defined personnel having prescribed qualification
Quality Risk Management (QRM)	A systematic process of assessment, control, communication and review of risk of the drug products.
Recall	The removal of specific batch/ batches of a therapeutic good/ product from the market for reasons relating to the quality, safety or efficacy and/ or if they are not in line with the particulars provided in registration/ enlistment application of the product.
Standard operating Procedure (SOP)	A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness.
Temperature	**Deep freeze**: Below -15 °C **In a refrigerator**: +2 to +8 °C **Cold or Cool**: +8 to + 15 °C **Room Temperature**: +15 to + 25 °C **Ambient**: The required storage temperature of non-refrigerated medicinal product; usually stated on the product as ‘store below 25 °C’ or ‘store below 30 °C’. **Labelled Temperature**: Any specific storage temperature required as per official monograph or Drug product label claim.
UPS	Uninterrupted power supply
Warranty	A quality assurance statement given by manufacturer or authorized distributor that pharmaceutical product complies with all applied condition of Act and rules.

7. QUALITY MANAGEMENT

The following sections provide core guidelines for the entities involved in the distribution and supply chain of pharmaceutical and biological products and recommends good practices to be adopted to maintain the quality, safety, and efficacy of drug products in the entire supply chain system. These guidelines are developed based on the PIC/s guide to Good Distribution Practices for Medicinal Products PE 011-1, Dated 1st June, 2014. EU Guidelines on Good Distribution Practice (GDP) of Drug Products for Human Use (2013/C 343/01) and WHO Guide to Good Storage Practices for Pharmaceuticals.

7.1. Principle

Distributors should develop and maintain a quality system setting out responsibilities, processes and risk management principles in relation to their activities. All distribution activities should be clearly defined in procedures and systematically reviewed. All critical steps of distribution processes and significant changes should be justified and where relevant validated. The quality system is the responsibility of the organization's management and requires their leadership and active participation and should be supported by staff commitment.

7.2. Quality System

The system for managing quality should encompass the organizational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the product delivered maintains its quality and integrity and remains within the legal supply chain during storage and/or transportation. The quality system should be fully documented and its effectiveness monitored. All quality system related activities should be defined and documented. A quality manual or equivalent documentation approach should be established.

If a main distributor/wholesaler is acting as a primary distributor, technical agreements should be in place with the marketing authorization holder (MAH). These technical agreements should at least describe the GDP roles and responsibilities of both parties including details on transportation arrangements, receipt of goods, batch release arrangements, verification of safety features, customer approval, documentation, recalls,

returns, customer complaints, suspected falsified medicinal products, and management of deviations and changes. The technical agreement serves as a basis for defining the division of GDP activities and responsibilities between the parties. However, it is important to highlight that the distributor/wholesaler retains ultimate responsibility for ensuring that the operations conducted are compliant with GDP and legal requirements. Any distributor/wholesaler operating to other accredited quality standards should ensure that its operation also complies with the legal requirement and GDP guidelines.

7.3. Management of Outsource Activities

The quality system should control and review of any outsourced activities related to the procurement, holding, supply, import or export of drug products. These processes should incorporate quality risk management.

7.4. Management Review and Monitoring

It is imperative that management is involved, provides adequate resources, and maintains oversight of GDP compliance. The management should have a formal process for reviewing the quality system on a periodic basis. The review should include:

i) Measurement of the achievement of quality system objectives.

ii) Assessment of performance indicators that can be used to monitor the effectiveness of processes within the quality system such as complaints, deviations, CAPA, changes to processes, feedback on the outsourced activities, self-assessment processes including risk assessments and audits, and external assessments such as inspections, findings and customer audits.

iii) Emerging regulations, guidance and quality issues that can impact the QMS.

iv) Innovations that might enhance the quality system.

v) Changes in business environment and objectives.

The outcome of each management review of the quality system should be documented in a timely manner and effectively communicated internally.

7.5. Quality Risk Management

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It is a valuable component of an effective quality system. Risk management may be used to

assess the risk posed to the product because of a deviation from normal practices or to justify a proposed deviation from accepted practice. The use of risk management should be based on scientific knowledge, reason and practices. The level of detail contained within the risk management process should be reflective of the level of risk to the product. Implications for product quality, security, traceability and follow-up actions should be detailed. Risk assessments should be carried out by competent personnel and should be reviewed and approved by relevant personnel, including the RP. Companies should have a procedure in place and training should be provided. All documentation for risk assessments performed should be available to an inspector during an inspection.

7.6. Change Control

The purpose of a change control system is to enable distributor/wholesaler to identify, document and assess changes that may impact compliance with GDP. Such changes may include, for example: a change in an insulated shipper used to transport cold chain products, a change in the settings of a heating system, or the relocation of a products storage area within a warehouse. Such changes may have a significant GDP impact and may have the potential to affect the quality of medicinal products distributed/ wholesaled. Therefore, it is vital that the change is conducted in a controlled manner.

A change control procedure to ensure that all changes to the operation are fully evaluated in terms of impact on product quality and traceability. The evaluation process should identify the areas impacted by the change, including processes, equipment, personnel, training, validation, quality system and regulatory implications. The required actions to give full effect to the change and ensure its implementation should be identified and assigned to relevant personnel. In addition, changes should be formally approved by the relevant managerial representative of the areas of the operation impacted by the change and by the responsible person (RP) prior to implementation. Changes should also be subjected to periodic review to ensure completion of actions which had been identified as required during the change control process.

7.7. Deviations, Investigations and Corrective and Preventive Actions (CAPA)

Deviations are non-conformances with quality system requirement of GDP, Applicable laws and, or in-house procedures. A procedure should be in place outlining the process for identifying, documenting, investigating, and closing deviations and the timelines

involved. Deviation investigations should aim to identify the root cause of the deviation. Corrective and preventive actions (CAPAs) may arise because of deviations, self-inspections, observations or from other incidents.

8. PERSONNEL

8.1. Principle

The correct distribution of medicinal products relies upon people. For this reason, there must be sufficient competent personnel to carry out all the tasks for which the wholesale distributor is responsible. Individual responsibilities should be clearly understood by the staff and be recorded.

8.2. Responsible Person

The distributor/wholesaler is required to appoint a management representative to act in the role of responsible person (RP). One of the qualified persons can be designated as RP or it can be another key member of staff accountable for ensuring that the quality, safety, and traceability of products is maintained within the supply chain. Several the GDP requirements may be delegated by the RP to other members of staff; however, they must personally:

i. Ensure that the quality system is implemented and maintained.
ii. Release returned products to saleable stock.
iii. Approve, sign and date all SOPs.
iv. Be involved in the approval of suppliers and customers.
v. Focusing on the management of authorized activities and the accuracy and quality of records.
vi. Ensuring that initial and continuous training programs are implemented and maintained.
vii. Coordinating and promptly performing any recall operations for drug products.
viii. Ensuring that relevant customer complaints are dealt with effectively.
ix. Ensuring that supplier and customers are approved.
x. Approving any subcontracted activities which may impact on GDP.
xi. Ensuring that self-inspections are performed at appropriate regular intervals following a prearranged program and necessary corrective measures are put in place.
xii. Keeping appropriate records of any delegated duties.
xiii. Deciding on the disposition of returned, rejected, recalled, or falsified products.

xiv. Approving any returns to saleable stock.
xv. Ensuring that any additional requirements imposed on certain products by national and provincial law are adhered to.

In addition, they should be involved in the process whereby any decision is made to quarantine or dispose of returned, rejected, recalled, or falsified products. This system should be in compliance with the guidance on rapid alert and recall system for defective therapeutic goods issued by the Drug Regulatory Authority of Pakistan. For returned products being disposed of, the RP need not approve each disposal but is required to maintain oversight of the process. The RP does, however, need to approve each return to saleable stock of are turned product. The marketing authorization holder should be involved in the decision-making process relating to recalls and suspected falsified medicinal products. The decision should be documented and recorded.

RPs should have sufficient pharmaceutical knowledge and experience to ensure full discharge of their responsibilities. Distributor/wholesaler should have precise criteria for the selection of suitable candidates for undertaking the role of RP. This should consider the complexity of the distribution/wholesale operation and the expertise and personal knowledge of the candidate. Key considerations in this regard are knowledge and understanding of:

i. The conditions of the distribution-wholesale authorization for which they are nominated.
ii. The products distributed/wholesaled under the authorization and the conditions necessary for their safe storage and distribution.
iii. Relevant provisions of the current applicable Acts and Rules pertaining to the distribution and wholesaling of drug products.

8.3. Training

All personnel involved in distribution/wholesale should be adequately trained on all activities and their training schedule should be regularly monitored and updated in line with the best international practices. They should have the appropriate competence and experience prior to commencing their tasks.

Personnel should receive initial and continuing training relevant to their role, based on written procedures and in accordance with a written training program. The personnel should also maintain their competence in GDP through regular training. In addition,

training should also include aspects of product identification and avoidance of falsified medicines entering the supply chain. A record of all training should be kept, and the effectiveness of training should be periodically assessed and documented.

8.4. Technical and Qualified Staff/Personnel

National/Provincial regulations relating to the qualifications and experience of personnel should be adhered to.

8.5. Specialized Trainings

Personnel dealing with hazardous pharmaceutical products (such as highly active materials, radioactive materials, narcotics, and other hazardous, environmentally sensitive and/or dangerous pharmaceutical products, as well as products presenting special risks of abuse, fire, or explosion) should be given specific training.

8.6. Specialized Clothing

Personnel involved in the distribution of pharmaceutical products should wear garments suitable for the activities that they perform. Personnel dealing with hazardous pharmaceutical products, including products containing materials that are highly active, toxic, and infectious or sensitizing, should be provided with protective garments as necessary.

8.7. Personnel Hygiene

Appropriate procedures relating to personnel hygiene, relevant to the activities to be carried out, should be established, and observed. Such procedures should cover health, hygiene, and clothing of personnel.

8.8. Personnel Record

Procedures and conditions of employment for employees, including contract and temporary staff, and other personnel having access to pharmaceutical products must be designed and administered to assist in minimizing the possibility of such products coming into the possession of unauthorized persons or entities.

8.9. Codes of Practice and Ethics

Ethical codes must be of practiced by the all the personnel involved in distribution and wholesale setups. Responsible person must have an oversight on the activities carried

out by the staff and any suspicious activity,or involvement in the distribution of unauthorized/suspected drug products, or found to be implicated in, any activities relating to the misappropriation, tampering, diversion or counterfeiting of any product, shall be stopped and immediately report to the relevant provincial and federal drug control authorities.

9. PREMISES AND EQUIPMENT

9.1. Principle

Distributor/wholesaler must have suitable and adequate premises, installations, and equipment to ensure proper storage and distribution of products in accordance to the applicable provincial rules for sale, storage and distribution of drug products. In particular, the premises should be clean, dry, and maintained within acceptable temperature limits.

9.2. Premises

The premises should be designed or adapted to ensure that the required storage conditions are maintained. They should be suitably secure, structurally sound and of sufficient capacity to allow safe storage and handling of the drug products. Storage areas should be provided with adequate lighting to enable all operations to be carried out accurately and safely.

The drug products should be stored in segregated areas which are clearly marked and have access restricted to authorized personnel. Any system replacing physical segregation, such as electronic segregation based on a computerized system, should provide equivalent security, and should be validated.

Products pending a decision as to their disposition or products that have been removed from saleable stock should be segregated either physically or through an equivalent electronic system. This includes, for example, any product suspected of falsification and returned products. Any suspected, falsified, expired, recalled and rejected products found in the supply chain should be immediately physically segregated and stored in a dedicated area away from all other products. The appropriate degree of security should

be applied in these areas to ensure that such items remain separate from saleable stock. These areas should be clearly identified.

Special attention should be paid to the storage of products with specific handling instructions as specified in DRAP's Act, drug product monographs or in summary of product characteristics (SmPC). Special storage conditions or special authorizations may be required for such products (e.g., narcotics and psychotropic substances with lock & key storage and separate record maintenance).

Receiving and dispatch bays should protect products from prevailing weather conditions. There should be adequate separation between the receipt and dispatch and storage areas. Procedures should be in place to maintain control of inbound/outbound goods. Reception areas where deliveries are examined following receipts should be designated and suitably equipped.

Unauthorized access to all areas of the authorized premises should be prevented. Prevention measures would usually include a monitored intruder alarm system and appropriated access control systems. Visitors should be accompanied.

Premises and storage facilities should be clean and free from litter and dust. Cleaning programs, instructions and records should be in place. Appropriate cleaning equipment and cleaning agents should be chosen and used so as not to present a source of contamination.

Premises should be designed and equipped to afford protection against the entry of insects, rodents, or other animals. A preventive pest control program should be in place.

Rest, wash, and refreshment rooms for employees should be adequately separated from the storage areas. The presence of food, drink, smoking material, or drug products for personal used should be prohibited in the storage areas.

9.3. Temperature and Environment Control

Suitable equipment and procedures should be in place to check the environment where drug products are stored. Environmental factors to be considered include temperature, light, humidity, and cleanliness of the premises.

An initial temperature mapping exercise should be carried out on the storage area before use, under representative conditions. Temperature monitoring equipment should be located according to the results of the mapping exercise, ensuring that monitoring

devices are positioned in the areas that experience the extremes of fluctuations. The mapping exercise should be repeated according to the results of a risk assessment exercise or whenever significant modifications are made to the facility or the temperature controlling equipment. For small premises of a few square meters which are at room temperature, an assessment of potential risks (e.g., heaters) should be conducted and temperature monitors placed accordingly.

9.4. Equipment

All equipment impacting on storage and distribution of drug products should be designed, located, and maintained to a standard which suits its intended purpose. Planned maintenance should be in place for key equipment vital to the functionality of the operation.

Equipment used to control or to monitor the environment where the products are stored should be calibrated at defined intervals based on a risk and reliability assessment.

Calibration of equipment should be traceable to an acceptable measurement standard. Appropriate alarm systems should be in place to provide alerts when there are excursions from pre-defined storage conditions. Alarm levels should be appropriately set, and alarms should be regularly tested to ensure adequate functionality.

Equipment repair, maintenance, and calibration operations should be carried out in such a way that the integrity of the medicinal products is not compromised.

Adequate records of repair, maintenance, and calibration activities for key equipment should be made and the results should be retained. Key equipment would include for example, cold storage units, monitored intruder alarms and access control systems, refrigerators, thermos-hygrometers, or other temperature and humidity recording devices, air handling units, and any equipment used in conjunction with the onward supply chain.

9.5. Computerized Systems

Before a computerized system is brought into use, it should be demonstrated, through appropriate validation, or verification studies, that the system can achieve the desired results accurately, consistently, and reproducibly.

A written, detailed description of the system should be available (may include diagrams also where appropriate). This should be kept up to date. The document should describe

principles, objectives, security measures, system scope and main features, how the computerized system is used and the way it interacts with other systems.

Data should only be entered into the computerized system or amended by persons authorized to do so. Data should be secured by physical or electronic means and protected against accidental or unauthorized modifications. Stored data should be checked periodically for accessibility. Data should be protected by backing up at regular intervals. Back up data should be retained for the period of at least five years at a separate and secure location. If the system fails or breaks down, there should be a written procedure to be followed for the restoration of data.

9.6. Qualification and Validation

Qualification is described as the action of proving that any equipment works correctly and leads to the expected results. Distributors should identify what key equipment qualification and / or key process validation is necessary to ensure correct installation and operation. The scope and extent of such qualification and / or validation activities (such as storage, pick and pack processes) should be determined using a documented risk assessment approach.

To qualify a piece of equipment, a written protocol should be generated outlining how the qualification will be conducted. The protocol should describe the piece of equipment along with its critical functions and attributes. The protocol should describe how the correct operation of these critical functions and attributes will be verified along with acceptance criteria. The protocol should be reviewed and approved by the RP. Following completion of the qualification exercise a report which cross-references the qualification and/or validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies.

Equipment and processes should be respectively qualified and / or validated before commencing use and after any significant changes e.g., repair or maintenance. A risk management approach should be applied. Risks may be calculated by identifying the event which may occur and then assessing the probability of occurrence, severity of occurrence and the degree of detection of the event. To validate a process, the

distributor/wholesaler should first of all clearly describe/map the process (including the use of diagrams/flowcharts where relevant).

Validation and qualification reports should be prepared summarizing the results obtained and commenting on any observed deviations. Deviations from established procedures should be documented and further actions decided to correct deviations and avoid their reoccurrence (corrective and preventive actions). The principles of CAPA should be applied where necessary. Evidence of satisfactory validation and acceptance of a process or piece of equipment should be produced and approved by appropriate personnel.

10. DOCUMENTATION

10.1. Principle

Good documentation constitutes an essential part of the quality system. Written documentation should prevent errors from spoken communication and permits the tracking of relevant operations during the distribution of products. Records should be made at the time each operation is undertaken.

10.2. Documentation

Documentation comprises all written procedures, instructions, contracts, records and data, in paper or in electronic form. Documentation should be readily available/ retrievable. It is required that documentation should be approved, signed and dated by designated persons, as required. It should not be handwritten; although, where it is necessary, sufficient space should be provided for such entries. Any alteration made in the documentation should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

Distribution of documents to staff should be controlled in a manner such that only up to date documents are available in relevant areas and obsolete copies should not be accessible. This may be achieved by maintaining a distribution list with records of procedures issued and retrieved, including the dates on which these activities took place. Superseded master copies of procedures should be maintained for a period of at least three (03) years.

Records must be kept either in the form of purchase/sales invoices, delivery slips, or on computer or any other form, for any transaction in drug products received or supplied. Records must include at least the following information: date; name of the drug product; quantity received, supplied; name and address of the manufacturers and supplier, customer, or consignee (as appropriate); and batch number, expiry date, as well as GTIN of drug product may be also stored for ready scanning and identification. Records are made contemporaneously and if handwritten, in clear, legible and indelible handwriting.

To ensure that procedures are maintained and are reflective of current GDP requirements, a periodic review should be performed. This review should be documented, and any recommendations should be implemented. It is particularly important that SOPs relating to activities in certain areas (e.g. receipt of material at the goods inwards area) are available to staff in the relevant area for reference as required. SOPs should describe the different operations which may affect the quality of the products.

In addition to those specified in the guidelines, there should be procedures in place for:

i. Training
ii. Documentation control
iii. Approval of suppliers and customers
iv. Order processing and deliveries
v. Waste management
vi. Self-inspection
vii. Change control
viii. Management review
ix. Quality risk management
x. Deviation management
xi. Corrective and preventive actions
xii. Other procedures may also include:
    a. Verification of safety features
    b. Decommissioning unique identifiers
    c. Staff sales
    d. Promotional samples and sales representatives
    e. Technical agreements
    f. Temperature mapping requirements
    g. Parallel importation
    h. Exempt/unauthorized products

i. Controlled drug management
j. Management of the cold chain

11. OPERATIONS

11.1. Principle

All actions taken by the distributors and wholesale establishments should ensure that the identity of the drug product is not lost and that the distribution of products is performed according to the information on the outer packaging. There should be use of all available means to minimize the risk of unauthorized / falsified drug products entering the legal supply chain, and only registered drug products with valid registration status shall be marketed. All key operations described below should be fully described in the quality system in appropriate documentation.

11.2. Qualification of Suppliers

Prior to the purchase and receipt of any drug product, distributors and wholesalers must verify compliance of the supplying manufacturer or its authorized distributor with the principles and guidelines of good distribution practices. This may include (but may not be limited to) verifying whether the supplying manufacturer have a valid Registration of drug product, Drug Manufacturing License and a current GMP certificate from DRAP, or in case of its authorized distributors holds a valid Drug Sales License. The authority of the supplier to supply medicinal products must be established. It is the responsibility of the distributor/wholesaler to establish this and to obtain appropriate documentary evidence. In this regard, systems should be in place to ensure that each supplier is legally entitled to supply a particular drug product.

A robust system for approval of new medicinal product suppliers is a key component in the prevention of falsified products entering the supply chain. In addition to establishing the authority of the supplier, distributors/wholesalers should reasonably assure themselves that previous stages in the supply chain are sufficiently robust to ensure the legitimacy of the products concerned. The links between the quality and purchasing functions within the distribution/wholesale operations are particularly important. Given the criticality of procedures for approving new suppliers in ensuring the quality and safety of drug products handled by the distribution/wholesale operation, it is expected

that the quality function maintain oversight of this process. In particular, the RP should be involved in the approval of new suppliers.

Distributors/ wholesalers are required to report to the Manufacturing Authorization Holder/ Manufacturer or Importer in case of issues which they consider suspicious or unusual with respect to the sourcing of drug products. Information of this nature is an important component in the protection of the legitimate supply chain for drug products.

11.3. Qualification of Customer

Distributors and wholesalers must ensure they supply drug products only to entities or persons who are possess of valid drug sale license, or authorized or entitled to supply drug products to the public or otherwise authorized to procure drug products from a distributor (for example healthcare institutions, drug products intended for clinical trials).

Distributors and wholesalers should monitor their transactions and investigate any irregularity in the sales patterns at risk of diversion (e.g. narcotics, psychotropic substances). Unusual sales patterns that may constitute diversion or misuse of drug product should be investigated and reported to relevant competent authorities.

11.4. New Product Introduction

Distributors/wholesalers should have a procedure in place relating to the introduction of new products to their inventory. This procedure should include a requirement to assess and document the regulatory system whether the product is registered through DRAP and under which the product has been classified (e.g., pharmaceutical product, biological, medical device, cosmetic, alternative medicines, nutraceuticals, etc.).Further categorization may also be documented (e.g., controlled drugs, over the counter preparations, prescription-only medicine, etc.), along with the required storage conditions and any additional requirements relating to their distribution.

11.5. Receipt of Products

The purpose of the receiving function is to ensure that the arriving consignment is correct, that the drug products originate from approved suppliers and that they have not been visibly damaged during transport.

If a drug product requires special handling, storage or security, measures should be taken to prioritize it, and once appropriate checks are completed it should be immediately transferred to appropriate storage facilities.

Batches of drug products should not be transferred to saleable stock before assurance has been obtained in accordance with written procedures, that they are authorized for sale.

If a falsified product is suspected, the batch should be segregated and should be reported to the relevant provincial drug control department and DRAP through Telephone:+ 92 51 9107317, 9107314, or email at; gsms@dra.gov.pk., along with MAH/ Manufacturer or Importer.

11.6. Storage

Drug products should be kept separate from other goods. Storage conditions are normally specified on the containers, for example 'Keep the container in the outer carton', 'Keep the container tightly closed', 'Store between 2 and 8°C', or '15-25°C', or 'Do not store above 25°C'. Products must be stored in accordance with the labelled conditions.

An initial temperature mapping exercise of the storage area must be performed and documented for areas greater than a few square meters. For areas less than a few square meters which are at room temperature, a risk assessment of the storage area can be conducted instead of a full mapping study.

To ensure that the appropriate conditions are maintained, continuous temperature monitoring probes/temperature data loggers should be located according to the results of the mapping exercise or risk assessment. This applies to all areas where drug products are stored (e.g., bulk storage, pick-face, quarantine and returns areas). At a minimum, a max/min type thermometer should be used. The maximum and minimum temperatures should be recorded every day and the thermometer reset after the readings have been taken. Temperature monitoring records should be reviewed and approved regularly to ensure compliance with the required storage conditions. Temperature excursions should be investigated immediately and documented. The manufacturer of the product should be consulted to ascertain the effect of any excursions from the labelled storage conditions. The method for investigating excursions should be described in a procedure.

Calibration certificates for temperature monitoring devices should be reviewed by the distributors/wholesalers to ensure that the accuracy of the devices is acceptable. Documentation should be available for inspection demonstrating that this review has occurred.

Incoming containers should be cleaned, if necessary, before storage. Any activities performed on the incoming goods (e.g. fumigation) should not impact on the quality of the drug products. Stock should be rotated according to the first expiry, first out (FEFO) principle. Products should be handled and stored in such a manner as to prevent spillage, breakage, contamination and mix-ups. Those products that are nearing their expiry date/shelf life should be withdrawn immediately from saleable stock.

Quarantined stock should be kept separate from approved stock. There should be a system in place to ensure that quarantined stock is not available for picking or returned to saleable stock inadvertently. An inventory of all quarantined product should be maintained and should include details such as date quarantined, batch numbers, expiry dates, quantities, reason for quarantining, disposition and date removed. This inventory may be maintained on a warehouse management system.

11.7. Pest Control

A pest control program should be in place. At a minimum this should include rodent control. Any recommendations made by a pest control service provider should be completed and recorded.

11.8. Supply

Prior to the dispatch of the pharmaceutical products, the supplier should ensure that the person or entity, e.g., transportation, is aware of the drug products to be distributed and complies with the appropriate storage and transport conditions. Controls should be in place to ensure the correct product is picked. The product should have an appropriate remaining shelf life when it is picked

11.9. Warranty Invoice

Written procedures for the dispatch of drug products should be established along with the generation of warranty invoice as per prescribed format on Form 2A under rule 19 and 30 of Drugs (Licensing, Registration and Advertising) Rules, 1976.

Records for the dispatch of drug products should be prepared and should include at least the following information:

i. Name of Drug product(s)
ii. Batch No(s) with manufacturing and expiry dates
iii. Dosage form
iv. Quantity
v. Date of dispatch
vi. Entity responsible for the transportation,
vii. Applicable transport and storage conditions
viii. Complete business name and address
ix. Status of the addressee (e.g., retail pharmacy, hospital etc.)
x. Telephone number and names of contact persons
xi. A unique number to allow identification of the delivery order

11.10. Cold Chain Practices

Delivery of products requiring controlled temperatures/cold chain should be in accordance with the applicable storage and transport conditions as per guideline of DRAP on Good Cold Chain Practices.

11.11. Product Disposal

All products that are rejected in house, rejected when received as returns or recalled should, if instructed accordingly by the MAH/Registration holder, be destroyed in an appropriate and timely manner and in accordance with the DRAP's guidelines and environmental guidelines. Certain products (e.g. narcotics and other controlled substances, etc.) may require special requirements for disposal that should be followed. The decision to dispose of products should be documented and recorded. Where the MA holder requests the return of waste product, this should be documented accordingly.

11.12. Imports and Exports

Drug products can only be imported by the registration holder or Authorized Indenters in accordance to the conditions of registration. DRAP has published a separate guideline for import and export activities of therapeutic goods which provide details on the eligibility for the importer and exporter, and illustrate the procedure, documentation and requirements to be fulfilled for import and export. An Online Import and Export System (OIES) is deployed by the DRAP to facilitate the therapeutic goods' industry for ease of

business and provision of conducive environment for compliance to regulatory requirement.

Necessary Storage and handling mechanism should be followed for clearance, offloading and transportation of imported pharmaceutical products form port of entry to warehouse.

12. COMPLAINTS, RETURNS, SUSPECTED FALSIFIED DRUG PRODUCTS AND RECALLS

12.1. Principle

All complaints, returns, suspected falsified products and recalls must be recorded and handled carefully according to written procedures. Records should be made available to the relevant provincial drug control departments and DRAP as required. An assessment of returned drug products should be performed by the qualified / responsible designated personnel before any approval for resale after consultation with MAH/ Manufacturer or Importer. A consistent approach by all stakeholders in the supply chain is required in order to be successful in the fight against falsified drug products.

12.2. Complaints

Distributors, wholesalers and other entities in supply chain should devise a complaint receiving and handling system. All complaints should be recorded with all the original details. A distinction should be made between complaints related to the quality of a drug product and those related to distribution, and others. In the event of a complaint about the quality of a medicinal product and a potential product defect, the manufacturer and/or marketing authorization holder as well as DRAP should be informed without delay.

If a defect relating to a drug product is discovered or suspected, consideration should be given to whether other batches of the product should also be investigated by manufacturer or Importer.

12.3. Management of Returned Products

A drug product should be considered as a ‘return’ once it has left the premises of the supplying distributor/wholesaler and subsequently returned to that premises. This may include the following examples:

i. Where a distributor/wholesaler supplies a customer with the incorrect product which is subsequently returned
ii. Where a customer returns a product to a distributor/ wholesaler which they ordered in error
iii. Where a product is received back to the premises of a distributor/wholesaler having never been received by the customer (e.g., because the customer's premises was closed).

Distributor/wholesaler should be extremely vigilant in their assessment of the suitability of returned products to be placed back into saleable stock. Once the returned product has been placed back into saleable stock it may not be possible to distinguish between the returned product and the remainder of the stock even if the batch number of the returned product was recorded.

When a return is received back it should be placed in a separate area so that there is no risk that it would be returned to saleable stock prior to assessment in error. This separate area should be clearly segregated from saleable stock (either by physical means or by a validated computerized system).All stages of the returns process should be documented. This documentation should allow all stages of the returns process to be traced including the person conducting each stage/activity. Distributors/wholesalers should pay particular attention to the time elapsed since the product was dispatched.

The qualified person / responsible person must approve returns to saleable stock. This approval should be documented and must occur prior to the product being placed back into saleable stock. If the product is to be rejected, then it should be placed into a reject area. There should be a register or log of returns in place which should include all product details and reasons for return. Personnel involved in the returns process should receive appropriate training and should have sufficient experience in relation to the handling of products to increase their ability to identify falsified drug products.

The distributor/wholesaler must ensure that the correct storage conditions have been maintained during the period the product was outside of the distributor's control. There must be no reasonable possibility that the storage conditions have been compromised during this period. Special care must be exercised with the return of any products containing controlled drugs or products requiring storage at low temperatures. Controlled drugs returned to distributor/wholesaler should immediately be identified

upon receipt and placed into a secure storage location. The time for which the product is outside of secure storage (e.g., during checking of the product) should be minimized.

12.4. Falsified Drug Products (Spurious, counterfeit)

Distributors/Wholesalers should be aware of the potential for falsified drug products (spurious, counterfeit) to enter the supply chain through the returns process. All relevant staff members should be made aware of this. It is imperative that all distributors/wholesalers operate using good governance and display vigilance in their efforts to prevent falsified drug products from being traded with other distributors/wholesalers or placed on the market.

Distributors and wholesalers must:

i. Have a procedure in place detailing the processes to be followed in the event of identifying a suspected falsified product or of being notified that a (suspected) falsified product has been received.
ii. Be aware of the possibility of falsified drug products being supplied in advertently through legitimate sources, i.e., other authorized distributors/wholesalers or returns from non-wholesale customers.
iii. Have robust systems for ensuring the legitimacy of their suppliers and ensure that these are regularly reviewed.
iv. Maintain a list of approved manufacturers/suppliers and ensure that products are only sourced directly from these approved manufacturers/suppliers.
v. Be familiar with the history of the supply chain for products received and question previous stages in the supply chain, if deemed necessary.
vi. Train staff to be aware of falsified products and what to look out for.
vii. Ensure that the goods-in procedure involves a detailed inspection of products received which can identify changes or unusual aspects to the appearance and packaging of products.
viii. Treat any offer of lower-cost product with suspicion. Distributors should pay particular attention to offers of low-cost products. As such, distributors should be familiar with the market price of the drug products they source and normal fluctuations in this price.
ix. Be vigilant and do not allow themselves to be used by counterfeiters to ‘launder’ falsified products.
x. If a single customer frequently buys or offers for sale suspiciously large quantities of the same product, no matter what the cost, then they may be acting in conjunction with the supplier of the product to pass falsified product through legitimate chains.
xi. Be knowledgeable of products at risk of counterfeiting.

xii. Ensure that drug products bearing safety features (2D barcodes, etc.) are verified as genuine.

A distributor/wholesaler in possession of a product that is found to be (or is suspected of being) falsified is responsible for the removal and quarantine of the product from saleable stock and for immediately informing the registration holder / the Marketing Authorization Holder and simultaneously to Drug Regulatory Authority of Pakistan through Telephone: + 92 51 9107317, 9107314, or email at; gsms@dra.gov.pk.

12.5. Recall

Through joint efforts with the registration holder, distributor/ wholesaler is obliged, in accordance with the applicable drug laws and DRAP's Guidelines on Recalls and Rapid Alerts of Defective Therapeutic Goods, to have a recall procedure in place. This is to enable the swift and effective recall from the marketplace of defective and/or potentially harmful drug products. In the event of a recall due to any Quality System related activity, the responsibility of the distributor/wholesaler will depend on whether they act as a primary or secondary distributor of the product in question.

Any recall operation should be recorded at the time it is carried out. Records should be made readily available to the regulators. The recall procedure should comply with the guidance issued by the Drug Regulatory Authority of Pakistan and at a minimum, should include the following:

i. The role of the RP / Qualified Person
ii. Nominated responsibilities for coordination of the recall action
iii. 24hr contact numbers for the company (at least three personnel) from the distributor and MAH to coordinate with DRAP
iv. Requirement to discuss with the MA holder, primary distributor/wholesaler (if any) and agree any action with the DRAP before recall action is carried out
v. The various classifications of a recall
vi. Description of the batch traceability system and method of identification of product recipients within the distribution chain (inducing the details of any standard documents or software packages that record such information)
vii. Method of handling recalled drug product
viii. Arrangements to ensure segregation of recalled products from saleable product
ix. Arrangements for return of recalled medicinal product to the MA holder
x. Procedure to be followed in the event of a quality defect being discovered on-site.

There should be an efficient and effective method for identifying customers supplied with a product subject to a recall along with templates of forms and letters for the

execution of a recall and to communicate appropriate degree of urgency and clear actionable instructions. If the product is exported, the overseas counterparts, and DRAP s must be informed to take measure accordingly.

The effectiveness of all recalls should be evaluated after the recall has concluded. Where the review of effectiveness identifies gaps in the process, those gaps should be appropriately addressed in a timely manner and the recall procedure revised accordingly in line with the guidelines issued by DRAP and best international practices.

13. OUTSOURCED ACTIVITIES

13.1. Principle

Any Quality System related activity covered by the GDP guide that is outsourced should be correctly defined, agreed, and controlled to avoid misunderstandings which could affect the integrity of the product. There must be a written contract between the contract giver and the contract acceptor which clearly establishes the duties of each party.

13.2. Contract Giver

The contract giver is responsible for the activities contracted out. The contract giver is responsible for assessing the competence of the contract acceptor to successfully carry out the work required and for ensuring by means of the contract and through audits that the principles and guidelines of GDP are followed. An audit of the contract acceptor should be performed before commencement of, and whenever there has been a change to the outsourced activities. The frequency of audit should be defined based on risk depending on the nature of the outsourced activities. The contract giver should provide the contract acceptor with all the information necessary to carry out the contracted operations in accordance with the specific product requirements and any other relevant requirements.

13.3. Contract Acceptor

The contract acceptor should have adequate premises and equipment, procedures, knowledge and experience, and competent personnel to carry out the work ordered by the contract giver.

The contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements and an audit of the third party by the contract giver. Arrangements made between the contract acceptor and any third party should ensure that the distribution information is made available in the same way as between the original contract giver and contract acceptor. The contract acceptor should refrain from any activity which may adversely affect the quality of the product(s) handled for the contract giver.

14. SELF INSPECTIONS

14.1. Principle

Self-inspection should be conducted to monitor implementation and compliance with GDP guidelines and to propose necessary corrective measures.

14.2. Self-Inspections

A self-inspection program should be implemented covering all aspects of GDP and compliance with this guideline. Self-inspections may be divided into several individual self-inspections of limited scope.

Self-inspections should be conducted in an impartial and detailed way by designated competent company personnel. Audits by independent external experts may also be useful but may not be used as a substitute for self-inspection. All self-inspections should be recorded. Reports should contain all the observations made during the inspection. A copy of the report should be provided to the management and other relevant persons. In the event that irregularities or deficiencies are observed, their cause should be determined, and the corrective and preventive actions (CAPA) should be documented and followed up.

15. TRANSPORTATION

15.1. Principle

It is the responsibility of the supplying distributors to protect drug products against breakage, adulteration, theft and to ensure that temperature conditions are maintained within acceptable limits during transport. Regardless of the mode of transport, it should be possible to demonstrate that the drug products have not been exposed to conditions

that may compromise their quality and integrity. A risk-based approach should be utilized when planning transportation.

15.2. Transportation

The required storage conditions for drug products should be maintained during transportation within the defined limits as described on the outer packaging and/or relevant packaging information. The distributor(s) must ensure that drug products are not subjected to prolonged periods of storage during transportation.

Where contract service providers are used, the distributor/wholesaler must make itself aware of the operating procedures of that party (e.g., by audit). This assessment should include examination of the transportation methods and routes. The distributor/wholesaler should be fully aware of, and agree to, any operations subcontracted to another party by the contract service provider. The contracted arrangements for transportation should be documented in a service level agreement and should include details of any sub-contracting.

15.3. Shipment Containers, Packaging and Labelling

All pharmaceutical products should be stored and distributed in shipment containers which do not have an adverse effect on the quality of the products, and which offer adequate protection from external influences, including contamination.

Shipping containers may not need to bear labels with full description of the identity of the container's content but should nonetheless provide sufficient information on handling and storage conditions and precautions to ensure the product is properly always handled.

The need for any special transport and/or storage conditions should be stated on the label. Only internationally and/or nationally accepted abbreviations, names or codes should be used in the labelling of containers.

Written procedures should be available for the handling of damaged and/or broken containers. Particular attention should be paid to those containing potentially toxic and hazardous products.

15.4. Products Requiring Controlled Conditions

In relation to deliveries containing drug products requiring special conditions such as narcotics or psychotropic substances, the wholesale distributor should maintain a safe and secure supply chain for these products in accordance with requirements laid down in national legislation. There should be additional control systems in place for delivery of these products. There should be a protocol to address the occurrence of any theft.

Radiopharmaceuticals should be transported in safe, dedicated and secure containers and vehicles.

For temperature-sensitive products, qualified equipment (e.g. thermal packaging, temperature-controlled containers or temperature-controlled vehicles) should be used to ensure correct transport conditions are maintained between the manufacturer, wholesale distributor and customer.

Special care should be used when using dry ice in containers. In addition to safety issues, it must be ensured that the pharmaceutical product does not come in contact with the dry ice, as it may have an adverse effect on the quality of the product.

15.5. Vehicles & Equipment for Transportation

Vehicles used to distribute, store, or handle pharmaceutical and biological products should be suitable for their use and appropriately equipped to prevent exposure of the products to conditions that could affect their stability and packaging integrity, and prevent contamination of any kind.

The design and use of vehicles must aim to minimize the risk of errors and permit effective cleaning and/or maintenance to avoid contamination, build-up of dust or dirt and/or any adverse effect on the quality of pharmaceutical products being distributed.

Vehicles, containers, and equipment should be kept clean and dry and free from accumulated waste. Measures should be in place to prevent unauthorized persons from entering and/or tampering with vehicles and/or equipment, as well as to prevent the theft or misappropriation thereof.

16. REFERENCES

i) The Drug Regulatory Authority of Pakistan, DRAP Act 2012.

ii) The Drugs Act 1976.

iii) The Drug (Licensing, Registering & Advertising) Rules 1976.

iv) EU Guidelines on Good Distribution Practice (GDP) of Medicinal Products for Human Use (2013/C 343/01).

v) PIC/s Guide to Good Distribution Practice for Medicinal Products.

vi) DRAP's Guidelines for Rapid Alter and Recall Arising from Quality Defects.

vii) DRAP's Guidelines for Import & Export.

viii) WHO Guide to Good Storage Practices for Pharmaceuticals.

ix) Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

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