MANUFACTURING & QUALITY AUDIT DIVISION

CENTRE FOR DRUG ADMINISTRATION

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GUIDANCE NOTES ON GOOD DISTRIBUTION PRACTICES

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GUIDANCE NOTES

Subject: GOOD DISTRIBUTION PRACTICES

A. Introduction

This guide is intended for those involved in the storage, transportation and distribution of starting materials and medicinal products. This guide applies to all steps in the entire distribution/supply chain.

The objective of the guide is to ensure that the quality and integrity of the product and material is maintained throughout the distribution chain. The manufacturers, agents, traders, brokers or distributors share important and distinctive roles and responsibilities to ensure that materials are of the required quality for their intended use.

This guide aims to describe the critical and important controls appropriate for the storage, trade and distribution of these materials. Not all of the controls described will be relevant to every situation. It is recognized that some of the controls are not applicable to certain companies or environment. The controls should be adapted to meet individual needs where necessary. The relevance of any control should be determined taking into consideration the specific risks the company is facing such that the desired standards of quality are achieved.

1 PERSONNEL

1.1 Key personnel in charge of warehousing functions should possess appropriate knowledge and experience, and where applicable, the relevant professional and technical qualifications for the tasks assigned to them.

1.2 Products or substances regulated under the Misuse of Drugs Regulations (i.e. Controlled Drugs) shall be placed under the direct supervision of a pharmacist registered with the Singapore Pharmacy Board.

1.3 All personnel should receive proper training in relation to GDP, current pharmaceutical legislations & regulations, operating procedures and safety issues, in accordance with a written training programme. Special training should be provided for personnel dealing with special

categories of materials such as cytotoxic, infectious or sensitizing products. Training records should be maintained.

2. PREMISES AND FACILITIES

2.1 Areas & General Description

2.1.1 Premises must have a permanent address and be located at a site approved by the relevant regulatory authority.

2.1.2 The storage of medicinal products should be carried out in buildings or parts of buildings that have been built for, or adapted to this purpose.

2.1.3 Buildings should protect products from contamination and deterioration, including protection from excessive heat or undue exposure to direct sunlight.

2.1.4 Buildings should have sufficient security to prevent unauthorized access and misappropriation of the goods.

2.1.5 Premises should be constructed, serviced and maintained regularly to protect stored materials, from all potentially harmful influences such as undue variations of temperature and humidity.

2.1.6 A separate receiving bay/area should be available. The receiving and dispatch area should be appropriately designed. They should protect materials from the weather. Receiving area should be designed and equipped to allow the cleaning of the containers of incoming materials, if necessary, before storage.

2.1.7 There should be adequate storage areas, and where applicable, physically separated zones for the orderly segregation of materials.

2.1.8 The storage areas should have adequate lighting and ventilation.

2.2 Cleanliness

2.2.1 The storage areas should be dry, clean and free of accumulated waste and dust. A written sanitation programme should be available indicating the frequency and methods to be used to clean the premises and areas.

2.2.2 Cleaning SOP(s) should be available and records should be kept of each cleaning.

2.3 Storage of Products

2.3.1 Materials should be stored off the ground and suitably spaced to permit cleaning and inspection. Pallets should be well maintained and kept in a good state of cleanliness.

2.3.2 There should be designated areas for quarantine, saleable stock, expired, rejected/damaged, recalled and returned products. Alternative means of segregation may be considered if proven to prevent mix-up.

2.3.3 The storage requirements under the regulations governing the storage of materials controlled under the Poisons Act (Poisons) and Misuse of Drugs Regulations (Controlled Drugs), and nationally/internationally-controlled psychotropic substances and narcotic drugs, must be taken into consideration.

2.3.4 Appropriate and suitable storage conditions should be provided for hazardous, sensitive and dangerous materials such as combustible liquids and solids, pressurised gases, highly toxic substances and radioactive materials/products.

2.3.5 Adequate precautions should be taken against spillage or breakage, attacked by microorganism, contamination and cross-contamination.

2.3.6 Materials requiring special storage conditions (e.g. temperature and/or humidity or narcotics requiring additional security measures) should be placed in separate areas constructed and equipped to provide the desired conditions. A list of such materials should be maintained and the materials properly identified.

2.3.7 Where controlled environmental storage conditions are required, these conditions should be continuously monitored and documented. Appropriate actions, on the premise, equipment and/or materials should be taken when the storage conditions are not met.

As far as possible, the actual storage temperature should be expressed quantitatively. Where the storage temperature is not expressed quantitatively or stated (in terms of a range) on the labels of the registered product the following definitions should be used as guidance:-

ON THE LABEL	GUIDANCE VALUES
Freezer	The temperature is thermostatically controlled between –20°C and –10°C
Refrigerator	The temperature is thermostatically controlled between 2°C and 8°C
Cold place	The temperature does not exceed 8°C
Cool place	The temperature is between 8°C and 15°C
Room temperature	The temperature is between 15°C and 30°C
Warm	The temperature is between 30°C and 40°C
Excessive heat	The temperature is above 40°C
Do not store over 30°C	The temperature is between 2°C and 30°C
Do not store over 25°C	The temperature is between 2°C and 25°C
Do not store over 15°C	The temperature is between 2°C and 15°C
Do not store over 8°C	The temperature is between 2°C and 8°C
Do not store below 8°C	The temperature is between 8°C and 25°C

Where storage conditions stated on the label means the following: -

ON THE LABEL	GUIDANCE VALUES
Protect from moisture	No more than 60% relative humidity in normal storage conditions; to be provided to the user in a moisture-resistant container
Protect from light	To be provided to the user in a light resistant container

2.3.8 Temperature of the storage areas must be measured at suitable predetermined intervals to show the maximum and minimum temperatures for the day and recorded. Where applicable, humidity measurements should also be performed.

2.3.9 It is recommended that temperature monitors be located in areas that are most likely to show fluctuations.

2.3.10 The instruments used for measuring and monitoring temperature and humidity should be calibrated or verified for accuracy and the results of such calibrations or verifications should be recorded and retained.

2.3.11 Materials in cartons/bulk packs should be adequately labeled for identification.

2.4 Pest Control

2.4.1 The storage area should be designed and equipped to prevent the entry of insects, rodents and other pests/animals.

2.4.2 There should be a pest control programme to identify and prevent pest infestation. Appropriate records should be kept.

3 STOCK HANDLING AND STOCK CONTROL

3.1 Receiving and Handling Products

3.1.1 Upon receipt, each incoming delivery should be checked against the relevant documentation and physically verified by label description, type and quantity, against the relevant purchase order information. The type and nature of checks should be stated in a written procedure.

3.1.2 All containers should be carefully inspected for tampering, contamination and damage and if necessary the suspected container or the entire delivery should be quarantine or set aside for further investigation.

3.1.3 Records should be retained for each delivery. They should include the description of the goods, quality, quantity, supplier, supplier's batch number, the date of receipt and assigned batch number. Where current regulations state a period for retention of records, this should be followed.

3.1.4 Secure measures should be taken to ensure that rejected products cannot be used and they should be stored separately from other products while awaiting destruction or return to the supplier. The measures adopted should possess adequate safeguards to prevent uncontrolled or unsatisfactory materials from being used or released.

3.2 Stock rotation and control

3.2.1 Comprehensive records should be maintained showing all receipts and issues of materials according to batch number.

3.2.2 Periodic stock reconciliation should be performed comparing the actual and recorded materials quantity. In any case, this should be performed when each batch is totally exhausted. All

significant stock discrepancies should be subjected to investigation to check for inadvertent mix-ups and wrong issues.

3.2.3 A system should be in place to ensure that materials due to expire first are sold and/or distributed first (Earliest-Expiry-First Out, EEFO). Where no expiry dates exist for the materials, FIFO (First-In-First-Out) should be applied. Deviations should, however, be permitted in exceptional cases where such as deviation is temporary and appropriate.

3.2.4 Materials with broken seals, damaged packaging or suspected of possible tampering/contamination must not be sold or supplied.

3.2.5 Materials bearing an expiry date must not be received or supplied after their expiry date or so close to their expiry date that this date is likely to occur before the materials are being used by the consumer.

3.2.6 All labels and containers of materials should not be altered, tampered or changed. The legislations relating to labels and containers should be adhered to at all times.

3.3 Deliveries to Customers

3.3.1 Written procedures on the delivery of materials to customers should be available.

3.3.2 There should be adequate provision for the security, storage condition and protection of the quality of materials during transportation to the customer. The transport process should not affect the integrity and quality of the materials.

3.3.3 Materials should be transported in such a way that:
a) their identification is not lost;
b) they do not contaminate, and are not contaminated by, other products or materials;

c) adequate precautions are taken against spillage, breakage or theft;
d) they are secure and not subjected to unacceptable degrees of heat, cold, light, moisture or other adverse influence, nor to attack by microorganisms or pests.

3.3.4 Materials requiring controlled temperature storage should be transported by appropriate or specialized means. Special care should be exercised when using dry ice during transportation. Materials should not come into contact with dry ice as this may cause freezing of the materials.

3.3.5 The use of devices to monitor temperature during delivery is recommended. Such records should be reviewed.

3.3.6 For deliveries of controlled drugs, requirements stipulated in the Misuse of Drugs Regulations should be followed.

3.3.7 Vehicles used should be adapted and maintained to suit the operations to be carried out. Vehicles should not be used as a store for materials.

4 DISPOSAL OF PRODUCTS

4.1 A written procedure on disposal of (expired, defective or rejected) pharmaceutical products should be available. Products containing Controlled Drugs must be destroyed or disposed of in accordance with the provisions of the Misuse of Drugs Regulations.

4.2 Disposal records should be maintained.

5 DOCUMENTATION

5.1 Types of Documentation

5.1.1 The documentation system should include the relevant SOPs and records, specifications of products/materials, and legal records. Any computerized document or format should comply with the current legislative requirements and/or international practices for electronic documentation and computerized systems. Records should be made available for convenient inspection.

5.2 Legal Records

5.2.1 Form E Record

This record is required under Rules 5(2) and 5(3) of the Poisons Rules for any wholesale sale or transaction of Poisons. The format is stipulated in the Eighth Schedule to the Poisons Rules.

The Record should include the following information:

- Date of Arrival/Sale
- Delivery Order/Sale Note Number
- Name & Address of Purchaser/Supplier
- Opening Stock
- Arrivals/Sales
- Stock Balance

5.2.2 Sales records

Sales records should be maintained for any wholesale sale of medicinal products.

A record of receipts and sales of the product shall be kept, stating the product name, pack size, date of transaction, invoice/delivery order number, name and address of

purchaser/supplier, batch number, expiry date, quantity received/sold and stock balance

This record may be combined with the Form E record if appropriate.

5.2.3 CD Register

A register shall be maintained for the transaction of all Controlled Drugs. This is a legal requirement under Regulations 14(1) & 14(2) of the Misuse of Drugs Regulations. The format for the register is stipulated in the Fifth Schedule to the Misuse of Drugs Regulations. The particulars to be recorded are as follows:

Entries to be made in case of obtaining:-

- Date on which supply was received
- Name/Address of person or firm from whom obtained
- Amount obtained
- Form in which obtained

Entries to be made in case of supply:-

- Date on which the supply was effected
- Name/Address of person or firm supplied
- Particulars as to licence or authority of person or firm supplied to be in possession
- Amount
- Form in which supplied
- Stock Balance (Receipts to be added in red)

Entries shall be made on the day on of transaction or, if that is not reasonably practicable, on the day next following that day.

No cancellation, obliteration or alteration of any such entry shall be made, and a correction of such an entry shall be made only by way of marginal note or footnote which shall specify the date on which the correction is made.

5.3 Documentation system

5.3.1 Procedures must be established and maintained for the development, control, distribution and review of all documents relating to the distribution process.

5.3.2 The title, nature and purpose of each document should be stated clearly. The contents of documents should be clear and unambiguous.

5.3.3 All documents should be completed, approved, signed and dated by an appropriate authorized person(s) and should not be changed without the necessary authorization.

5.3.4 Document should be reviewed regularly and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version.

5.3.5 All records must be readily retrievable, stored and retained.

5.4 Electronic Records

5.4.1 Data, especially legal records, may be recorded by electronic data processing systems but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked.

5.4.2 A written detailed description of the system should be produced (including diagrams as appropriate) and kept up to date. It should describe the principles, objectives, security measures and scope of the system and the main features of the way in which the computer is used and how it interacts with other systems and procedures.

5.4.3 Only authorised persons should be able to enter or modify data in the computer. Access should be restricted by passwords or

other means. User should have a unique identifier (User ID) for their personal and sole use so that activities can subsequently be traced to the responsible individual.

5.4.4 There should be a record of changes and deletions. Any alteration to an entry of critical data should be authorised and recorded with the reason for the change. Consideration should be given to the system creating a complete record of all entries and amendments (an "audit trail").

5.4.5 Records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper or other means, at regular intervals. It is particularly important that the data, including audit trail, are readily available throughout the period of retention. Back-up data should be stored as long as necessary at a separate and secure location.

6 PRODUCT COMPLAINTS

6.1 Written procedure describing the actions to be taken in the handling of all written and oral complaints regarding a material should be available. There should be a record for each individual complaint.

6.2 The procedure for handling complaints shall ensure that the complaints received are investigated and followed through, that corrective actions are taken to prevent repeated complaints, and, where a decision is made to recall the product, the details of the recall.

6.3 Within the company a person shall be designated to handle complaints. This person must have the authority to initiate investigations. All investigations should be documented in writing.

6.4 If a product defect is discovered or suspected in a batch, consideration should be given to determine whether other batches are also affected.

6.5 The investigation should take into consideration the condition and circumstances under which the product was distributed, stored and used.

6.6 An investigation report must be put up with all corrective/preventative actions clearly stated.

6.7 Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention.

7. PRODUCT RECALL

7.1 An emergency plan for urgent recalls and a non-urgent product recalls procedure should be described in writing.

7.2 A person or committee should be designated for the co-ordination and execution of all product recalls.

7.3 In the event of a recall, all customers to whom the product has been distributed shall be informed with the appropriate degree of urgency.

7.4 The recall message should indicate whether the recall need to be carried out at the retail level, and whether there is a need to remove all recalled products immediately from the shelves, and prevent their mixing with other saleable stocks.

7.5 Local regulatory authority should be informed for all recalls. If the material is exported, the overseas counterparts and/or regulatory authorities must be informed of the recall.

7.6 Where recall affects a particular batch, consideration should also be given to determine whether other batches/materials are also affected.

7.7 All actions taken in connection with the recall must be approved by the company and/or regulatory authorities, and recorded.

7.8 Reconciliation should be made between delivered and recovered quantities of materials.

8 RETURNED MATERIALS

8.1 Written procedures describing the handling returned materials and the corresponding records of all returns should be kept.

8.2 All returned products should be kept apart from saleable stock to prevent redistribution until a decision has been reached regarding their disposal.

8.3 Materials should only be returned to saleable stock if:

a) the materials are in their original unopened containers and in good condition;
b) it is known that the materials have been stored and handled under proper conditions;
c) the remaining shelf life period is acceptable; and
d) the goods have been examined and assessed by appropriate personnel. This assessment should take into account the nature of the product, any special storage conditions required, and the time which had elapsed since it was distributed. Special attention should be given to thermo-labile products. Advice should be sought from the marketing authorization (product licence) holder or manufacturer as necessary.

8.4 The returned materials should be formally released to saleable stock by a nominated, responsible person following a satisfactory quality re-evaluation.

8.5 Products returned to saleable stock should be placed in accordance with the EEFO/FIFO system.

9 COUNTERFEIT PRODUCTS

9.1 Any counterfeit materials found in the distribution network should be physically segregated from other materials to avoid any confusion. They should be clearly labeled as “Not for Sale” or other similar phrases/words.

9.2 The regulatory authority and the holder of the marketing authorisation of the original product should be informed immediately.

10 SELF-INSPECTION

10.1 An SOP on self-inspection stating the persons involved in self-inspection, the frequency and the criteria should be maintained.

10.2 Self inspections are conducted and recorded in order to monitor the implementation and compliance with Good Distribution Practices (GDP) standard.

11. CONTRACT ACTIVITIES

11.1 Any activities performed, referenced in the GDP guideline and delegated to another party, should be agreed upon in a contract.

11.2 There should be a written and approved contract or formal agreements between the contract giver and contract acceptor that addresses and defines in detail the responsibilities and GDP requirements for each party.

11.3 The contract should permit the Contract Giver to visit the facilities of the Contract Acceptor.

11.4 Depending on the nature of activities performed, the Contract Acceptor should understand that he might be subject to inspection by the regulatory authority.

12. Handling of Active Pharmaceutical Ingredient or Intermediates

12.1 This section are additional requirements which are relevant the agents, brokers, traders or distributors, generally referred to as “dealer”) who may trade and/or take possession, distribute or store an API or intermediate.

12.2 Active Pharmaceutical Ingredient (API) is any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

12.3 Intermediate is a material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API.

12.4 The dealers should maintain complete traceability of APIs and intermediates that they distribute. Documents that provides traceability includes identity and address of the original manufacturer, purchase orders, transportation documentation, manufacturer’s batch number, transportation and distribution records as well as authentic Certificates of Analysis.

12.5 Original certificates of analysis issued by the manufacturer or authenticated copies of the original certificates of analysis should be provided for each batch of intermediates or APIs on request by the customers

REFERENCES

1. Rules and Guidance for Pharmaceutical Manufacturers and Distributors 1997. London: The Stationery Office.
2. Good Storage Practice. World Health Organization 2000.
3. EU Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03)
4. Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice (GMP) for Medicinal Products.
5. PIC/S GMP Guide for Active Pharmaceutical Ingredients
6. The Medicines Act and its subsidiary legislations.
7. The Poisons Act and Rules.
8. The Misuse of Drugs Regulations.

END OF DOCUMENT

GUIDANCE NOTES

Subject: GOOD DISTRIBUTION PRACTICES

General points to consider for auditor and auditee

- **General Information**
  - Any contract warehouse(s)
  - Approval available for the use of the warehouse
  - Identify products that require re-packing/labelling

- **Personnel**
  - Name and designation of personnel
  - Training programme and records

- **Premises and Facilities**
  - Floor area
  - Layout plan
  - Store approval
  - Adequate storage area with segregations
  - Appropriate for the products
  - Lights/ventilation

- **Cleanliness**
  - Dry and clean
  - Cleaning programme
  - Cleaning records

- **Storage of products**
  - Storage off ground
  - Segregation
  - Precautions against deterioration
  - Storage – Sunlight; Security
  - Identify materials that require special handling
  - Thermometer / hygrometer and recording
  - Cold storage
  - Materials labelled
  - Written procedure on storage and distribution

- **Pest Control**
  - Appropriate programme

- **Receiving and Handling**
  - Procedure
  - Appropriate types of checks conducted
  - Distribution records and duration of storage

- **Stock Rotation and Control**
  - EEFO / FIFO
  - Stock Reconciliation

- **Deliveries**
  - Written procedure
  - Security; Storage condition; Protection
  - Specialised means for special products

- **Disposal**
  - Written procedure and evidence of disposal

- **Documentation**
  - Documentation system
  - SOP signed and formalized
  - Computerised record
  - Poison labels
  - Legal record
    - Form E / Sales Records
    - CD Register (Part I & II)
    - Sample Control Record
    - Signed order and Invoices

- **Product Complaints**
  - SOP and records
  - System for investigation and review

- **Recall**
  - SOP and records
  - Designated person
  - Level of recall established

- **Returned Goods**
  - SOP and records
  - Assessment criteria
  - Authorization for re-sale

- **Self Inspection**
  - SOP and records

- **Availability of procedures and records**
  - Training
  - Cleaning / Sanitisation
  - Pest Control
  - Receiving, handling, delivery and disposal
  - Complaints
  - Recalls
  - Returns
  - Self Inspection

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REVISION HISTORY

Rev No.	DCC Ref No.	Author	Date of Revision	Remarks of Revision
001	-	-	01 Nov 2001	New document.
002	-	-	09 Dec 2002	Update document format.
003	218	Terrance Ong	01 Mar 2004	1) Change 3D HSA logo to 2D HSA logo. 2) Change Centre name to Centre for Drug Administration 3) Detached Revision History from Guidance Notes.
004	266	Terrance Ong	06 Sep 2004	1) Re-located Revision History to the main document.
005	310	Peh Eng Chin	01 Jan 2005	The new revision involves numerous changes and requirements. The major and significant changes are highlighted below 1) Subject title changed from “Guidance Notes on Good Distribution Practices for Medicinal Products” to “Guidance Notes on Good Distribution Practices”. 2) Inclusion of introductory paragraph and summarized Points-to-Consider for Inspection 3) New requirements for training of staff, maintaining sales records, documentation system, electronic recordings, contract activities and handling of API/Intermediates 4) System of FIFO and EEFO 5) Protection of materials during deliveries