HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

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GOOD MANUFACTURING PRACTICE FOR ASSEMBLERS OF THERAPEUTIC PRODUCTS

HSA
Health Sciences Authority

Foreword: This document serves to provide guidance to Assemblers of Therapeutic Products but it is not meant to replace the PIC/S Guide to Good Manufacturing Practice (GMP) For Medicinal Products. The PIC/S Guide to Good Manufacturing Practice (GMP) For Medicinal Products (Part I) would be the standard used during the GMP audit of all manufacturers (including assemblers) of medicinal products.

Scope: All licensed manufacturers which are involved in assembly of therapeutic products.

Definition: Assemble, in relation to a therapeutic product, means enclosing the product in a container which is labeled before the product is sold or supplied (primary packaging), or where the product is already enclosed in a container in which it is to be sold or supplied, labeling the container before it is sold or supplied (secondary packaging). Assembly has a corresponding meaning.

1. GENERAL DESIGN AND CONSTRUCTION

1.1 The size of assembly area must reflect the volume of assembly. The adequacy of the working space should permit the orderly and logical positioning of equipment and materials so as to avoid confusion and to minimize the risk of cross-contamination between different medicinal products or their components.

1.2 Premises for assembly of products should be specifically designed, constructed, and laid out to avoid product mix-up and cross-contamination.

1.3 The interior surfaces (walls, floors and ceilings) of the assembly area should be smooth, free from cracks and open joints, should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection. Cleaning of the premises and, where applicable, disinfection, should be carried out according to written procedures.

1.4 Assembly areas should be well-lit and effectively ventilated, with air handling system (including temperature, humidity and filtration controls) where appropriate.

1.5 Rest and refreshment rooms should be separate from assembly areas. No consumption of food should be allowed in the assembly and storage areas.

1.6 Adequate toilet facilities must be available and must be kept clean and in good order. Toilets must not in any case open

directly into the assembly or storage areas. Toilet areas must not be used for storage or as a source of water for assembly.

2. WAREHOUSE

Storage Area

2.1 There should be adequate storage areas with general good house-keeping.

2.2 Segregated areas should be provided for the storage of approved, quarantined, rejected, recalled and returned materials or products.

Pest Control

2.3 The storage areas should be designed and equipped to prevent the entry of insects, rodents and other animals.

2.4 There should be a pest control programme to control the entry of insects, rodents and other animals. Appropriate records should be kept.

2.5 The equipment, materials and products should be protected against chemical contamination in the course of the pest control operation.

3. MATERIALS CONTROL

Products to be re-packed

3.1 Medicinal products should only be purchased from approved suppliers named in the relevant specifications and, where possible, directly from the producer. A batch certificate of analysis should be obtained from the supplier for each batch of product to be re-packed.

3.2 For each delivery, the containers should be checked for integrity of package and seal, for correspondence between the delivery note and the supplier's labels, and for compliance with product quality specifications and shipment conditions (where applicable)

3.3 Containers of incoming materials should be cleaned where necessary before storage.

3.4 Damage to containers or packaging materials or any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.

3.3 Medicinal products in the storage area should be appropriately labeled. There should be appropriate procedures or measures to assure the identity of the contents of each container of the products. Bulk containers from which quantities of the products have been drawn should be clearly identified.

3.4 Products requiring special storage conditions should be placed in separate areas constructed and equipped to provide the desired conditions. The storage conditions should be continuously monitored and recorded.

3.5 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 apply:-

ON THE LABEL	MEANS
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 should 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

For other non-quantitative labeling, the following definitions should apply :-

ON THE LABEL	MEANS
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

3.6 Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labeled containers.

Packaging Materials

3.7 The purchase, handling and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials. Only materials which have been inspected and released by the Quality Control Department should be used.

3.8 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorized access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorized personnel following an approved and documented procedure.

3.9 Each delivery or batch of printed or primary packaging materials should be given a specific reference number or identification mark.

3.10 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and the disposal recorded.

3.11 When setting up a programme for the packaging operations, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

4 GOOD ASSEMBLY PRACTICES

Special Considerations

4.1 The appropriate marketing authorization of the product(s) to be assembled shall be complied with, and where necessary, the approval of the holder of the market authorization and licensing authority shall be sought.

4.2 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the primary assembly of these categories of medicinal products:

(a) Highly sensitizing materials, for example, penicillins and cephalosporins.
(b) Biological preparations, for example, preparation of live microorganisms.

(c) Cytotoxics, steroids, hormonal products and other high risk antibiotics.

4.3 All products and materials used for assembly should be checked before use by a designated person for quantity, identity and conformity with the packaging instructions. Line clearance should be performed prior to commencement of the assembly operation.

4.4 Each batch of products produced must be assigned a unique batch number.

4.5 All containers used for filling should be cleaned according to a written procedure. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

4.6 Normally, filling and sealing should be followed as quickly as possible by labeling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabeling can occur.

4.7 The correct performance of any printing operation (for example batch number coding and expiry dating) which is carried out separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.

4.8 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

4.9 On-line control of the product during packaging should include at least checking the following:

(a) General appearance of packages;
(b) Completeness of packages;
(c) Correctness of products and packaging materials used;
(d) Correctness of over-printing, e.g. batch number, expiry date.

4.10 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

4.11 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

4.12 Where any packaging process validation applies, the study should be carried out in accordance with pre-defined and authorized protocols.

Assembly Equipment

4.13 Assembly equipment/apparatus should be cleaned according to detailed and written procedures and stored only in a clean and dry condition. These equipment/apparatus should not present any hazard to the products. The parts that come into contact with the products must not be reactive, additive or absorptive to such an extent that it will affect the quality of the products and thus present any hazard.

4.14 Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

5 DOCUMENTATION

General Requirements

5.1 Documents should be designed, prepared, reviewed and distributed with care. They should be approved, signed and dated by appropriate and authorized persons

5.2 Documents should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.

5.3 Handwritten entries should be made in clear, legible, indelible way.

5.4 Records should be made or completed at the time each action is taken and in such a way that all significant activities are traceable.

5.3 Any alteration made to the entry on a document 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.

Assembly Documents

5.4 A Batch Assembly Record should be kept for each batch or part batch assembled. The record should carry the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained.

5.5 The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the assembly/manufacture of medicinal products are traceable. They should be retained for at least one year after the expiry date of the finished products.

5.6 All starting and packaging materials used in the assembly process should have approved specifications which serve as the basis for quality evaluation.

5.7 Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data processing methods, only authorized persons should be able to enter or modify data in the computer and there should be a record of changes and deletion; access should be restricted by passwords or other means and the result of entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper or other means. It is particularly important that the data are readily available throughout the period of retention.

5.8 The assembly instructions should include:

(a) Name of product;
(b) Description of its pharmaceutical form, and strength where applicable;
(c) The pack size expressed in terms of the number, weight or volume of the product in the final container;
(d) A complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
(e) Where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf-life of the product;Special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
(f) A description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
(g) Details of any in-process controls with instructions for sampling and acceptance limits

5.9 Before any assembly begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use.

5.10 Written receipt, release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by the authorized person(s) designated for the purpose.

5.11 Records should be maintained for the distribution of each batch of the product in order to facilitate the recall of the batch if necessary.

Batch Packaging Record

5.12 A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions and should contain the following information:

(a) The name, batch number and expiry date of the product;
(b) The date(s) and times of the packaging operations;
(c) Identification (initials) of operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;
(d) Records of checks for identity and conformity with the packaging instructions, including the results of in-process controls;
(e) Details of the packaging operations carried out, including references to equipment and the packaging lines used;
(f) Whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;
(g) Notes on any special problems or unusual events including details, with signed authorization for any deviation from the Packaging Instructions,;
(h) The quantities and reference number of identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation.
(i) Approval by the person responsible for the packaging operations.

6 STOCK HANDLING AND STOCK CONTROL

Stock Rotation and control

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

6.2 Periodic stock reconciliation should be performed comparing the actual and recorded stocks. In any event, this should be performed when each batch is totally used up. All significant stock discrepancies should be subjected to investigation as a check against inadvertent mix-ups and wrong issues.

6.3 Issues should normally observe the principle of stock rotation, i.e. first-in-first-out.

6.4 Products with broken seals, damaged packaging or suspected of possible contamination must not be sold or supplied.

6.5 Goods 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 goods are used by the customer.

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

Delivery of Finished Products

6.7 Before delivery, each consignment should be checked against the relevant documentation and physically verified by label description, type and quantity, against the order.

6.8 All containers should be carefully inspected for contamination and damage and if necessary they should be cleaned or set aside for further investigation. Records mandated by current laws and regulations should be retained for each delivery for the legally required period.

6.9 Products containing Controlled Drugs must be destroyed or disposed of in accordance with the provisions of the Misuse of Drugs Regulations.

Cold Chain Products

6.10 For handling of cold chain products, please refer to the requirements found in the HSA Guidance Note on Good Distribution Practice.

7 REJECTED AND RETURNED GOODS

Rejected Goods

7.1 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should be either returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by the authorized personnel.

7.2 The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. Record should be kept of the reprocessing.

Returned Goods

7.3 There should be a Standard Operating Procedure (SOP) for handling returned products. Records of all returns goods should be kept.

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

7.5 Products should only be returned to saleable stock if:

(a) The goods are in their original unopened containers and in good conditions;
(b) It is known that the goods 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 a personnel responsible. 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.

7.6 The returned products should be formally released to the saleable stock by the authorized person.

8 PRODUCT COMPLAINTS

8.1 An SOP describing the actions to be taken in the handling of all written and oral complaints regarding a product should be available. The SOP should 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.

8.2 There should be a record for each individual complaint.

Investigations

8.3 The person responsible for handling complaints should initiate the investigation immediately and all investigation should be documented in writing. The investigation should take into consideration the condition and circumstances under which the product was distributed, stored and used.

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

8.5 An investigation report should be put with all corrective/preventive actions clearly stated.

9 PRODUCT RECALL

9.1 There should be an SOP for all urgent and non-urgent product recalls.

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

9.3 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.

9.4 If the product is exported, the overseas counterparts and/or regulatory authorities must be informed of the recall.

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

10 QUALITY CONTROL

10.1 There should be a designated and independent personnel in charge of Quality Control (QC).

10.2 Finished product assessment should embrace all relevant factors, including assembly conditions, product testing if any, a review of packaging documentation, compliance with finished

product specification and visual examination of the final finished pack. Where product testing is involved, the analytical method(s) should be validated before routine use.

10.3 The samples taken should be done in accordance with approved written procedures that describe:
(a) The method of sampling;
(b) The equipment to be used;
(c) The amount of the samples to be taken
(d) The storage conditions for the samples taken

10.4 Any in-process controls, including those carried out in the assembly area, should be approved by QC and the results recorded.

11 SELF INSPECTION

11.1 Self inspections should be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice principles and to propose necessary corrective measures.

11.2 Personnel matters, premises, equipment, documentation, assembly, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls should be examined at intervals following a pre-arranged programme in order to verify their conformity with the principles of Quality Assurance.

11.3 Self inspections should be conducted in an independent and detailed way by designated competent person from the company. Independent audits by external experts may also be useful.

11.4 All self-inspection should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.

12 PERSONNEL

12.1 Adequate training should be provided for all personnel whose activities could affect the quality of the final products. Training programmes should be available. Visitors or untrained personnel should, preferably, not be taken into the assembly area.

12.2 All personnel should also receive periodic medical examination. Steps should be taken to ensure as far as is practical that no person affected by an infectious disease or having open lesions

on the exposed surface of the body is engaged in the assembly operations.

12.3 Every person entering the assembly area should wear protective overalls appropriate to the operations carried out. Direct contact should be avoided between the operator's hands and the exposed product as well as any part of the equipment that comes into contact with the products.

References

1. PIC/S Guide to Good Manufacturing Practice For Medicinal Products
2. HSA Guidance Note on Good Distribution Practice (GUIDE-MQA-013)

END OF DOCUMENT

HEALTH SCIENCES AUTHORITY

Health Products Regulation Group
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