

Annex 9

Guide to good storage practices for pharmaceuticals¹

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1. Introduction

This guide is intended for those involved in the storage, transportation and distribution of pharmaceuticals. It is closely linked to other existing guides recommended by the WHO Expert Committee on Specifications for Pharmaceutical Preparations, such as:

- Good trade and distribution practice (GTDP) of pharmaceutical starting materials (1);
- The stability testing of pharmaceutical products containing well-established drug substances in conventional dosage forms (information given in connection with regulation for marketing authorization) (2);
- Good manufacturing practices (GMP) (3);

¹ This guidance has been prepared in close collaboration with the International Pharmaceutical Federation (FIP).

- The cold chain, especially for vaccines and biologicals;
- *The International Pharmacopoeia (4)*.

The objective of this guide is to supplement the above-mentioned documents by describing the special measures considered appropriate for the storage and transportation of pharmaceuticals. However, they may be adapted to meet individual needs where necessary, provided that the desired standards of quality are still achieved.

The guidelines are applicable not only to manufacturers of medicinal products but also to pharmaceutical importers, contractors and wholesalers, and community and hospital pharmacies. They should be adjusted in line with the type of activity where the storage of pharmaceuticals is taking place. National or regional regulations should be followed for all related activities.

2. **Glossary**

The definitions given below of some of the terms used in this document take into account the terminology of current regulations and recommendations.

active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used in the production of a drug, becomes an active ingredient of that drug. 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.

contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a starting material, or intermediate or finished product during production, sampling, packaging or repackaging, storage or transport.

cross-contamination

Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

excipient

A substance, other than the active ingredient, which has been appropriately evaluated for safety and is included in a drug delivery system to:

- aid in the processing of the drug delivery system during its manufacture;
- protect, support or enhance stability, bioavailability, or patient acceptability;
- assist in product identification; or
- enhance any other attribute of the overall safety and effectiveness of the drug during storage or use.

expiry date

The date given on the individual container (usually on the label) of a drug product up to and including which the product is expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf-life to the date of manufacture.

labelling

The action involving the selection of the correct label, with the required information, followed by line clearance and application of the label.

manufacture

All operations of purchase of materials and products, production, quality control, release, storage and distribution of finished products, and the related controls.

material

A general term used to denote starting materials (active pharmaceutical ingredients and excipients), reagents, solvents, process aids, intermediates, packaging materials and labelling materials.

packaging material

Any material, including printed material, employed in the packaging of a pharmaceutical product, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

pharmaceutical product

Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

production

All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

retest date

The date when a material should be re-examined to ensure that it is still suitable for use.

storage

The storing of pharmaceutical products and materials up to their point of use.

supplier

A person providing pharmaceutical products and materials on request. Suppliers may be agents, brokers, distributors, manufacturers or traders. Where possible, suppliers should be authorized by a competent authority.

3. Personnel

3.1 At each storage site (e.g. that of a manufacturer, distributor, wholesaler, community or hospital pharmacy) there should be an adequate number of qualified personnel to achieve pharmaceutical quality assurance objectives. National regulations on qualifications should be followed.

3.2 All personnel should receive proper training in relation to good storage practice, regulations, procedures and safety.

3.3 All members of staff should be trained in, and observe high levels of, personal hygiene and sanitation.

3.4 Personnel employed in storage areas should wear suitable protective or working garments appropriate for the activities they perform.

4. Premises and facilities

Storage areas

4.1 Precautions must be taken to prevent unauthorized persons from entering storage areas.

4.2 Storage areas should be of sufficient capacity to allow the orderly storage of the various categories of materials and products, namely starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.

4.3 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required on the label (e.g. temperature, relative humidity), these should be provided, checked, monitored and recorded. Materials and pharmaceutical products should be stored off the floor and suitably spaced to permit cleaning and inspection. Pallets should be kept in a good state of cleanliness and repair.

4.4 Storage areas should be clean, and free from accumulated waste and vermin. A written sanitation programme should be available indicating the frequency of cleaning and the methods to be used to clean the premises and storage areas. There should also be a written programme for pest control. The pest-control agents used should be safe, and there should be no risk of contamination of the materials and pharmaceutical products. There should be appropriate procedures for the clean up of any spillage to ensure complete removal of any risk of contamination.

4.5 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials and pharmaceutical products to be cleaned, if necessary, before storage.

4.6 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing physical quarantine should provide equivalent security. For example, computerized systems can be used, provided that they are validated to demonstrate security of access.

4.7 There should normally be a separate sampling area for starting materials in a controlled environment. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination. Adequate cleaning procedures should be in place for the sampling areas.

4.8 Physical or other equivalent validated (e.g. electronic) segregation should be provided for the storage of rejected, expired, recalled or returned materials or products. The materials or products, and areas concerned should be appropriately identified.

4.9 Highly active and radioactive materials, narcotics and other hazardous, sensitive and/or dangerous materials and pharmaceutical products, as well as substances presenting special risks of abuse, fire or explosion, (e.g. combustible liquids and solids and pressurized

gases) should be stored in a dedicated area that is subject to appropriate additional safety and security measures.

4.10 Materials and pharmaceutical products should be handled and distributed according to GMP as defined in this document.

4.11 Materials and pharmaceutical products should be handled and stored in such a manner as to prevent contamination, mix-ups and cross-contamination.

4.12 Materials and pharmaceutical products should be stored in conditions which assure that their quality is maintained, and stock should be appropriately rotated. The “first expired/first out” (FEFO) principle should be followed.

4.13 Rejected materials and pharmaceutical products should be identified and controlled under a quarantine system designed to prevent their use until a final decision is taken on their fate.

4.14 Narcotic drugs should be stored in compliance with international conventions, and national laws and regulations on narcotics.

4.15 Broken or damaged items should be withdrawn from usable stock and separated.

4.16 Storage areas should provide adequate lighting to enable all operations to be carried out accurately and safely.

Storage conditions

4.17 Storage conditions for pharmaceutical products and materials should be in compliance with the labelling, which is based on the results of stability testing (see Appendix).

Monitoring of storage conditions

4.18 Recorded temperature monitoring data should be available for review. The equipment used for monitoring should be checked at suitable predetermined intervals and the results of such checks should be recorded and retained. All monitoring records should be kept for at least the shelf-life of the stored material or product plus 1 year, or as required by national legislation. Temperature mapping should show uniformity of the temperature across the storage facility. It is recommended that temperature monitors be located in areas that are most likely to show fluctuations.

4.19 Equipment used for monitoring should also be calibrated at defined intervals.

5. **Storage requirements**

Documentation: written instructions and records

5.1 Written instructions and records should be available which document all activities in the storage areas including the handling of expired stock. These should adequately describe the storage procedures and define the route of materials and pharmaceutical products and information through the organization in the event of a product recall being required.

5.2 Permanent information, written or electronic, should exist for each stored material or product indicating recommended storage conditions, any precautions to be observed and retest dates. Pharmacopoeial requirements and current national regulations concerning labels and containers should be respected at all times.

5.3 Records should be kept for each delivery. They should include the description of the goods, quality, quantity, supplier, supplier's batch number, the date of receipt, assigned batch number and the expiry date. Where national regulations prescribe that records must be retained for a certain period, this must be observed. (Otherwise such records should be retained for a period equal to the shelf-life of the incoming materials and products, where applicable, plus 1 year).

5.4 Comprehensive records should be maintained showing all receipts and issues of materials and pharmaceutical products according to a specified system, e.g. by batch number.

Labelling and containers

5.5 All materials and pharmaceutical products should be stored in containers which do not adversely affect the quality of the materials or products concerned, and which offer adequate protection from external influences. In some circumstances, this could include bacterial contamination.

5.6 All containers should be clearly labelled with at least the name of the material, the batch number, the expiry date or retest date, the specified storage conditions and reference to the pharmacopoeia, where applicable. Unauthorized abbreviations, names or codes should not be used.

Receipt of incoming materials and pharmaceutical products

5.7 On receipt, each incoming delivery should be checked against the relevant purchase order and each container physically verified, e.g. by the label description, batch number, type of material or pharmaceutical product and quantity.

5.8 The consignment should be examined for uniformity of the containers and, if necessary, should be subdivided according to the supplier's batch number should the delivery comprise more than one batch.

5.9 Each container should be carefully inspected for possible contamination, tampering and damage, and any suspect containers or, if necessary, the entire delivery should be quarantined for further investigation.

5.10 When required, samples should be taken only by appropriately trained and qualified personnel and in strict accordance with written sampling instructions. Containers from which samples have been taken should be labelled accordingly.

5.11 Following sampling, the goods should be subject to quarantine. Batch segregation should be maintained during quarantine and all subsequent storage.

5.12 Materials and pharmaceutical products should remain in quarantine until an authorized release or rejection is obtained.

5.13 Measures should be taken to ensure that rejected materials and pharmaceutical products cannot be used. They should be stored separately from other materials and pharmaceutical products while awaiting destruction or return to the supplier.

Stock rotation and control

5.14 Periodic stock reconciliation should be performed by comparing the actual and recorded stocks.

5.15 All significant stock discrepancies should be investigated as a check against inadvertent mix-ups and/or incorrect issue.

5.16 In manufacturing facilities, partly used containers of materials and pharmaceutical products should be securely reclosed and resealed to prevent spoilage and/or contamination during subsequent storage. Materials and pharmaceutical products from containers which have been opened or partly used should be used up before those in unopened containers.

5.17 Damaged containers should not be issued unless the quality of the material has been shown to be unaffected. Where possible, this should be brought to the attention of the person responsible for quality control. Any action taken should be documented.

Control of obsolete and outdated materials and pharmaceutical products

5.18 All stocks should be checked regularly for obsolete and outdated materials and pharmaceutical products. All due precautions should be observed to prevent the issue of outdated materials and pharmaceutical products.

6. Returned goods

6.1 Returned goods, including recalled goods, should be handled in accordance with approved procedures and records should be maintained.

6.2 All returned goods should be placed in quarantine and returned to saleable stock only after this has been approved by a nominated, responsible person following a satisfactory quality re-evaluation.

6.3 Any stock reissued should be so identified and recorded in stock records. Pharmaceuticals returned from patients to the pharmacy should not be taken back as stock, but should be destroyed.

7. Dispatch and transport

7.1 Materials and pharmaceutical products should be transported in such a way that their integrity is not impaired and that storage conditions are maintained.

7.2 Special care should be exercised when using dry ice in cold chains. In addition observing to safety precautions, it must be ensured that the materials or product does not come in into contact with dry ice, as this may adversely affect the product quality, e.g. by freezing.

7.3 Where appropriate, the use of devices to monitor conditions such as temperature during transportation is recommended. Monitoring records should be available for review.

7.4 The dispatch and transport of materials and pharmaceutical products should be carried out only after receipt of a delivery order. The receipt of the delivery order and the dispatch of the goods must be documented.

7.5 Dispatch procedures should be established and documented, taking into account the nature of the materials and pharmaceutical products concerned and any special precautions that might be required.

7.6 The outside container should offer adequate protection from all external influences and should be indelibly and clearly labelled.

7.7 Records for dispatch should be retained, stating at least:

- the date of dispatch;
- the customer's name and address;
- the product description, e.g. name, dosage form and strength (if appropriate), batch number and quantify;
- the transport and storage conditions.

7.8 All records should be readily accessible and available on request.

8. Product recall

8.1 There should be a procedure to recall from the market, promptly and effectively, pharmaceutical products and materials known or suspected to be defective.

References

1. *Good trade and distribution practice (GTDP) of pharmaceutical starting materials*. Geneva, World Health Organization, 2002 (unpublished document QAS/01.014; available on request from Essential Drugs and Medicines Policy, World Health Organization, 1211 Geneva 27, Switzerland).
2. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996 (WHO Technical Report Series, No. 863).
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4. *The international pharmacopoeia*, 3rd ed. Vol. 1: General methods of analysis; Vol. 2: Quality specifications; Vol. 3: Quality specifications; Vol. 4: Tests, methods, and general requirements. Quality specifications for pharmaceutical substances, excipients, and dosage forms; Volume 5: Test and general requirements for dosage forms. Quality specifications for pharmaceutical substances and tablets (in press). Geneva, World Health Organization, 1979–2002.

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Appendix

Storage and labelling conditions²

Normal storage conditions

Storage in dry, well-ventilated premises at temperatures of 15–25°C or, depending on climatic conditions, up to 30°C. Extraneous odours, other indications of contamination, and intense light must be excluded.

Defined storage instructions

Drug products that must be stored under defined conditions require appropriate storage instructions. Unless otherwise specifically stated (e.g. continuous maintenance of cold storage) deviation may be tolerated only during short-term interruptions, for example, during local transportation.

The use of the following labelling instructions are recommended:

| <i>On the label</i> | <i>Means</i> |
|--------------------------|---|
| “Do not store over 30°C” | from +2°C to +30°C |
| “Do not store over 25°C” | from +2°C to +25°C |
| “Do not store over 15°C” | from +2°C to +15°C |
| “Do not store over 8°C” | from +2°C to +8°C |
| “Do not store below 8°C” | from +8°C to +25°C |
| “Protect from moisture” | no more than 60% relative humidity in normal storage conditions; to be provided to the patient in a moisture-resistant container. |
| “Protect from light” | to be provided to the patient in a light-resistant container. |

² The text was adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its 34th meeting (*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-Fourth report*. Geneva, World Health Organization, 1996, Annex 5 (WHO Technical Report Series No. 863).