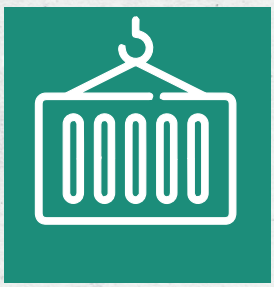
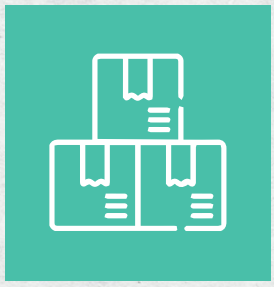
REPUBLIC OF LEBANON
MINISTRY OF PUBLIC HEALTH

GOOD COLD CHAIN MANAGEMENT FOR TEMPERATURE-SENSITIVE PHARMACEUTICAL PRODUCTS



01.Containers and containers labeling

02.Transportation practices & temprature monitoring during transportation



03.Storage building

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01 Introduction

In order to maintain product quality, safety and efficacy during distribution, Good Distribution and Storage Practices specify that temperature-sensitive products are to be stored, handled and distributed carefully throughout the distribution network.

Environmental controls play a key role in maintaining drug safety, quality and efficacy. Temperature is one of the most important parameters to control. Drugs must be stored, and transported according to predetermined conditions as supported by stability data. Temperature excursions outside of their respective labeled storage conditions, for brief periods, may be acceptable provided stability data and scientific/technical justification exists demonstrating that product quality is not affected.

This annex is issued, to complete the Lebanese Good Storage and Distribution Practices of pharmaceutical products, by the Lebanese Ministry of Health, which stresses the importance of adhering to it by all parties involved in any aspect of the cold chain, as relevant to the particular role that they play, from the premises of the manufacturer of the product to the person dispensing or providing pharmaceutical products directly to a patient or his agent.

Year	Page- Section	Revision	Description of Main Changes
2024	Page 9 – Chapter 3	3	Further requirements related to returned cold chain products
	Page 16 – Chapter 6		Introduction of a chapter related to the management of power failure
	Page 18 – Chapter 7		Introduction of a chapter related to management of complaints and product recall

02 Glossary

The definitions provided below apply to the words and sentences used on these guidelines:

Cold chain
The system of transporting and storing vaccines within the safe temperature range of °2+C to °8+C. [4

Storage temperature
The temperature range listed on the TTSPP label, and within the regulatory documentation, for long- term storage. [3]

Temperature-modified
Includes any environment in which the temperature is predictably maintained at a level different from that of the surrounding environment, but is not actively or passively controlled within precise redefined limits. [3]

Temperature-sensitive pharmaceutical product
Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended. [3]

Validation
Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria. [3]

Temperature excursion
An excursion event in which a TTSPP is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data. [3]

Temperature-controlled
Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits. [3]

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. [3]

1.Containers & containers labeling

1.1 Any controlled transport and/or storage conditions as well as warning statements (for example, «Time and Temperature Sensitive», «Do Not Freeze») should be clearly stated on the label applied to shipping containers. This label should be securely affixed and indelible. The label and shipping documents should clearly state that these products should be transferred without delay to the specified storage temperature upon receipt. [1]

1.2 Shipping containers should be qualified to meet the expected extremes of ambient temperature within the distribution environment, if they provide the primary means of environmental control for the drug product. [1]

1.3 Selection of a shipping container and/or box should be based on:
-The storage and transportation requirements of the drugs
-The space required for the volume of drugs to be transported
-The anticipated extremes of ambient temperature
-The estimated maximum length of time required for transportation of the drugs including any in transit storage [1]

1.4 When warm/cold packs are placed in containers used to transport drugs:
-The type, size and number of packs should correspond to the shipping duration and temperature needed
-The location of the packs should ensure that the entire shipment of the product is maintained within the labeled storage conditions
-Adequate barrier materials should be used to prevent contact between the packs and the products, if the packs are at a temperature outside the range acceptable for product storage [1]

1.5 The use of dry ice in the transportation of drugs must not adversely affect the drug product or the primary package. [1]

2.Transportation practices and temperature monitoring during transportation

2.1 Temperature-sensitive products must be transported in a manner that ensures the products will be maintained within an acceptable temperature range as defined in the approved labeling and supported by stability data. [1]

2.2 Temperature excursions outside of their respective labeled storage conditions, for brief periods, may be acceptable provided stability data and scientific/technical justification exists demonstrating that product quality is not affected. Procedures shall be in place to address similar situations. [1]

2.3 The transportation process and containers should be designed to prevent damage and maintain the integrity and quality of the drug products. For example, transport conditions for ampoules should limit their exposure to physical stress to avoid the development of hairline cracks. [1]

2.4 Written procedures for the shipping of drug products should be established. Such procedures should take into account the nature of the drug products, local conditions, modes of transport and any seasonal variations experienced, as well as describe any special handling precautions. [1]

2.5 These procedures should be qualified to ensure that appropriate conditions are maintained under probable extremes of ambient temperature and should also account for possible unforeseen delays which may occur in shipping/transportation (for example, delays at the border). [1]

2.6 Refrigerated vehicles/transportation containers should be mapped and monitored, if they provide the primary means for environmental control. However, this may not be necessary if a qualified insulated container/package or an appropriate temperature monitoring device on the package or selected packages, or gel packs or similar approved means, or lane profile data is used as the primary means of environmental control. [1]

2.7 Temperature and humidity monitoring devices, such as data loggers, should be calibrated at predetermined intervals. Single use monitoring devices should be qualified (for example, verification of performance for indicator strips or freeze indicator units). [1]

2.8 Transportation practices by carriers, including any storage and/or transportation activities performed by sub-contractors, should be verified by reviewing documentation. A record of the review should be kept and any discrepancies should have a follow up. [1]

2.9 Loading activities (loading and unloading) should be done in a manner that preserves the quality of the drugs. [1]

2.10 Shipments temporary stored at port of entry should be preserved in a secure warehouse under the conditions recommended by the product manufacturer, until the shipment has been authorized for removal by customs, in order to avoid risk of theft or damage during temporary storage. [3]

2.11 Draw up procedures and memoranda of understanding to ensure that these shipments are cleared through customs as rapidly as possible. [3]

2.12 Vehicles and equipment used to distribute, store, or handle drugs should be suitable for their use and appropriately protective of the products to prevent exposure to conditions that could affect their stability and packaging integrity, as well as prevent contamination of any kind. [1]

2.13 Special storage conditions (temperature, humidity, others) required for the cold chain, should be provided, checked, monitored and recorded within vehicles. Temperature mapping of vehicles should support uniformity of the temperature across the vehicle. Recorded temperature monitoring data should be available for review. [1]

3.Storage buildings

3.1 The warehouse should provide perimeter protection to ensure security of the grounds and storage buildings against anticipated risks, in order to protect against vandalism, theft and other illegal incursions. Security arrangements should be appropriate to the site location and the value of goods stored there. [3]

3.2 The warehouse should keep the site free of accumulated dust, dirt, waste and debris. Pests should be kept under control within the site area. Waste should be collected in designated closed containers and arranged for safe disposal at frequent intervals. [3]

3.3 The warehouse should provide suitable fire detection and fire-fighting equipment, including fire hydrants where possible, in all temperature-sensitive products storage areas and ensure that:
-Systems and equipment are appropriate for the class of occupancy and product storage arrangements
-Equipment is regularly serviced in accordance with the equipment manufacturers' recommendations and local regulations
-Fire prevention, detection and control standard operating procedures are documented
-Staff is trained and fire drills are regularly carried out
-Smoking is prohibited in all areas [3]

3.4 The warehouse should ensure that receiving and dispatch bays are designed to avoid conflict between incoming and outgoing goods and are protected from direct sunlight, dust, dirt, rain, snow and wind, and from extremes of heat, cold and solar radiation that could damage the products and measures should be taken to minimize pest activity in these areas. [3]

3.5 Deliveries should be examined at receipt in order to check that containers are not damaged and that the consignment corresponds to the order. [1]
3.6 Pharmaceutical products are promptly transferred to an appropriate warehousing area where cautions are taken to avoid that any non-authorized individuals enter warehousing areas. [1]
3.7 Drug distributors must maintain records and inventories that show receipt and distribution or "other disposition" of prescription drugs. These records must include the source of the drugs, the address of the location that the drugs were shipped from, the identity and quantity, and the dates of receipt/ distribution/other disposition. Records must be kept and easily identifiable. [1]

3.8 The warehouse should provide a quarantine area for the isolation of returned, faulty, recalled and otherwise withdrawn goods pending a decision on disposal or re-stocking by the qualified person or department. Materials within quarantine areas must be clearly identified with their status:

-With temperature control, for items returned for re-stocking

-With temperature control, for items recalled for testing

-Without temperature control, for items awaiting disposal.

The quarantine area may be a physically separated zone, or it may be defined using a suitable stock control information system, or by a combination arrangement. Written procedure(s) shall be in place to ensure the appropriate management of products in quarantine status. [3]

3.9 Cold-chain products may only be returned to saleable stock where there is no reasonable possibility that the cold-chain has been compromised. For example, under the following circumstances, the return of product could be considered:

- The batch number of the distributed product is known, and was recorded by the wholesaler.
- The entire process is validated (i.e. delivery to customer, opening of the packaging, examination of the product, returning of the product to the packaging and sealing of the packaging, collection by the courier/transporter, and return to the distribution site refrigerator).

Alternatively, return of cold-chain products could be considered where there is a unique monitoring system attached to the product which would demonstrate whether the product has been stored outside refrigerated conditions.[5]

4.Storage conditions control & monitoring in storage

4.1 The warehouse should provide thermostatic temperature control systems for all temperature controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store temperature-sensitive products. [3]

4.2 Temperature monitoring systems and devices should comply with the following minimum requirements:

-Monitoring sensors accurate to ± 0.5 °C or better for electronic devices and ± 1 °C or better for alcohol, bi-metal gas or vapor pressure thermometers.

-Monitoring sensors calibrated

-Monitoring sensors located in areas where greatest variability in temperature is expected to occur within the qualified and/or tested storage volume

-Monitoring sensors positioned so as to be minimally affected by transient events such as door opening

-Temperature monitoring devices, temperature traces or electronic temperature records manually checked at least twice a day, in the morning and evening, seven days a week, including public holidays [3]

4.3 Temperature-controlled rooms, cold rooms and freezer rooms should:

-Provide a temperature record with a minimum recording frequency of six times per hour for each monitoring sensor position

-Provide documentation for each monitoring sensor position which can be stored and accessed

-Continue to operate independently in the event of a power failure [3]

4.4 Refrigerators and freezers used to store drugs should:

-Be well maintained

-Be equipped with alarms

-Be free from excessive frost buildup

-Allow for adequate air distribution and orderly storage within the chamber

-Storage practices and loading configurations should not lead to the obstruction of air distribution

-Have sensors for continuous monitoring and alarms located at the points representing the temperature worst case scenarios

-Be calibrated as required by the calibration program

-Be equipped with a backup power source or have alternate storage available in the event of a power failure: it is preferable to connect refrigerators and freezers to a multipoint monitoring system with a minimum recording frequency of six times per hour for each sensor position which can operate independently in the event of a power failure. Alternatively the warehouse can use battery-powered portable temperature monitoring devices with a minimum recording frequency of six times per hour. The least preferred option is a thermometer or maximum/minimum thermometer. Documentation should be provided for each appliance which can be stored and accessed.

-Be of commercial grade and not be of household type, unless they incorporate the above controls . The use of household type refrigerators and freezers is discouraged. [2] [1]

4.6 More specifically, for temperature-sensitive products which are adversely affected by high relative humidity and are not sufficiently protected by their packaging. Such products are typically labeled “store in a dry place”, or carry similar wording and require a humidity-controlled environment which should be provided by the warehouse. [3]

Humidity control and monitoring

4.7 The warehouse should provide humidity monitoring systems and devices in temperature-controlled rooms that are used to store temperature-sensitive products which require a humidity-controlled environment, complying with the following minimum requirements:

-Sensors accurate to ± %5 RH

-Sensors calibrated

-Sensors located to monitor worst-case humidity levels within the qualified storage volume

-Sensors positioned so as to be minimally affected by transient events such as door opening

-Humidity records should be provided with a minimum recording frequency of six times per hour for each sensor position;

-Documentation should be available for each sensor position which can be stored and accessed

-Continue to operate independently in the event of a power failure [3]

4.8 The warehouse should provide temperature alarm systems for temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store temperature-sensitive products. [3]

4.9 The warehouse should provide humidity alarm systems for temperature-controlled rooms used to store temperature-sensitive products that require a humidity-controlled environment. [3]

Cleanliness of temperature-controlled stores.

4.10 The warehouse should implement a cleaning and decontamination program for all temperature controlled rooms:

-Floor areas are fully accessible for cleaning

-Goods are not stored directly on the floor

-Storage is not permitted for any non-pharmaceutical products except transport-related items such as icepacks, gel packs and the like

-No accumulation of dust, dirt and waste, including packaging waste

-Precautions are taken against spillage or breakage, and cross-contamination

-No accumulation of frost and ice, particularly ice contaminated by spillages

-Waste is collected in designated closed containers and arrange for safe disposal at frequent intervals

-Cleaning records are available to demonstrate compliance [3]

Refrigeration equipment maintenance

4.11 The warehouse should implement a maintenance program for all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers:

-Carry out regular planned preventive maintenance on all temperature controlling equipment.

-Make arrangements to ensure that emergency maintenance is carried out within a time period that does not place temperature-sensitive products at risk of damage

-Ensure that there is a contingency plan to move products stored in nonfunctioning equipment to a safe location before damage to the product occurs in the event that equipment cannot be repaired in a timely manner

-Maintain records to demonstrate compliance [3]

Calibration of temperature control and monitoring devices

4.12 The warehouse should calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified. Calibration should demonstrate the accuracy of the unit across the entire temperature range over which the device is designed to be used. Single-use devices that are supplied with a manufacturer's calibration certificate do not need to be re-calibrated. [3]

Calibration of humidity control and monitoring devices.

4.13 The warehouse should calibrate devices against a certified, traceable reference standard at least once a year unless otherwise justified. Single-use devices that are supplied with a manufacturer's calibration certificate do not need to be re-calibrated. [3]

Alarm equipment verification

4.14 The warehouse should check functionality of temperature and humidity alarms at least once every six months at the designated set points and should maintain records to demonstrate compliance. Appropriate procedures shall be in place. [3]

4.15 Written procedures should be available describing the actions to be taken in the event of temperature excursions outside the labeled storage conditions. All excursions outside the labeled storage conditions must be appropriately investigated and the disposition of the stock in question must be evidence-based (for example, stability data and technical justification). [3]

5.Personnel training

5.1 All personnel involved in the distribution activities should be competent on the basis of appropriate training in the requirements of cold chain and the handling of temperature sensitive products. [1]

5.2 Personnel training on cold chain requirements should be based on written standard operating procedures (SOPs). They should receive initial and continuing training relevant to their tasks, in accordance with a written training program covering at least:

-Applicable pharmaceutical legislation and regulations

-SOPs and safety issues

-Response to emergencies [3] [1]

5.3 Trainings should be assessed as applicable to evaluate the effectiveness of the actions taken. Appropriate records should be maintained, including details of subjects covered and participants trained. [1]

6.Managing a Power Failure

Power failures occur for many reasons. How a power failure is managed in your organization may depend on the cause of the power outage, whether prior notice was given and the time of day the outage occurs. The safety and wellbeing of staff should always be considered when managing power failures, particularly when they occur outside business hours.[4]

6.1 A backup plan should be put in place, if a power failure occurs. This will allow vaccines to continue to be stored between the recommended temperatures of °2+C and °8+C, thereby minimizing vaccine loss and disruption to your facility's activities.

Alternative vaccine storage in the event of a power failure should include any of the following:

• a back-up power supply (eg generator or battery/solar back-up)

• a monitored refrigerator offsite (eg at a local hospital or pharmacy) to ensure that an agreement has been put in place with the relevant organization before the event, and also consider that this organization may be affected by the same power failure

• a cooler, each facility should ensure that they have enough coolers for an emergency.[4]

6.2 If during business hours, power goes off, immediately isolate the vaccines and keep them refrigerated between °2+C and °8+C. Leave the vaccines in the refrigerator with the door closed and put a sign on the refrigerator door stating: 'Power out. Do not use vaccines. Keep refrigerator door closed.' [4]

6.3 The temperature of the refrigerator should be closely monitored, using a battery-operated thermometer or portable data logger.[4]

6.4 If the temperature rises to °8+C, vaccines should be moved to a prepared cooler, cold box or portable purpose-built vaccine refrigerator. Ensure that all vaccines are packed and monitored with a digital minimum/maximum thermometer or data logger.[4]

6.5 Vaccines should never be transported from one vaccine refrigerator to another, without a data logger to monitor the temperature. Domestic refrigerators (including bar fridges) are not built or designed to store vaccines and must not be used for vaccine storage. If there is no suitable alternative monitored storage option, isolate the vaccines and leave them in the refrigerator with the door closed for the duration of the power outage. [4]

6.6 If there is a power failure outside normal business hours, such as during a storm, the safety, health and wellbeing of staff should be the main priority. Depending on the temperature-monitoring and alarm systems in use, an alert may be sent to the registered user by text message or email. The alerted staff member can take action, if safe to do so, to prevent vaccine losses.[4]

6.7 When power is returned, the minimum and maximum refrigerator temperatures should be recorded, the refrigerator temperature should be reset in case the temperature reaches 8+ °C or less. The temperature should be between °2+C and °8+C before returning vaccines. The refrigerator should be monitored hourly to ensure that the temperature is consistently stable, then return to twice-daily monitoring.[4]

7.Management of Complaints and Product Recall

7.1 Complaints regarding a medicine or its packaging, as distinct from those relating solely to matters within the wholesaler›s control, should be directed promptly to the supplier or sponsor of the medicine. [6]

7.2 Complaints relating to the wholesaler›s own activity, including transport, should be evaluated. Unless the evaluation indicates that the problem is trivial or outside the wholesaler›s control, measures should be taken to remedy the problem and prevent its recurrence. Records of these complaints and the remedial measures taken should be maintained.[6]

7.3 Temperature-sensitive products which have left the care of the wholesaler should only be returned to saleable stock if examined and assessed by a person authorized to do so and:

a.they are in their original unopened containers, with intact labels and packaging and bear a valid expiry date; and

b.there is no reason to believe that they have been subject to adverse environmental conditions; and

c.there is no reason to believe the goods have been tampered with or are contaminated; and

d.on receipt, they are packed separately from other goods and accompanied by a separate Returns Note; and

e.if necessary, advice is sought from the sponsor of the medicines [6]

7.4 Medicines not returned to saleable stock should be quarantined pending disposal, or returned in accordance with the agreement between the wholesaler and the supplier or sponsor.[6]

7.5 Recalls carried out should be documented and records of all recalled medicines received into the warehouse should be kept.[6]

7.6 Stock that has been recalled and is not immediately destroyed should be placed in quarantine until disposal so that it cannot be sold in error or leak and contaminate other goods.[6]

7.7 Standard operating procedures should be in place to ensure all recalled medicines are accounted for until disposal occurs.[6]

8.Documentation & SOPs

8.1 When commercial carriers are used, all pertinent conditions should be specified in a written agreement between the distributor, importer or wholesaler, and the third-party. The contractors should comply with the written agreement. [1]

8.2 Distributors, importers and wholesalers should maintain transportation records of inbound and outbound shipments, including monitoring records where applicable, for a period of one year after expiry date of the product. [1]

8.3 Records of investigations and actions taken in the event of excursions outside predetermined temperature conditions, as per labeled storage conditions are kept for a minimum of one year after the expiration date of the product. [1]

8.4 Documents, and in particular instructions and procedures relating to any activity within the cold chain that could have an impact on the quality of pharmaceutical products, should be designed, completed, reviewed and distributed with care. They must be available at all time and reviewed regularly. [1]

8.5 SOPs should cover: methods for pharmaceutical products requiring specific warehousing conditions; drug orders and shipments preparation (including a description of the shipping configuration of the protective package used and taking into consideration the requirements for labeling, sealing and warning for the shipping / warehousing); use of equipment and instruments related to the cold chain (refrigerator, cold room, controllers, etc.); calibration of monitoring and regulation instruments dedicated to cold chain equipment; corrective actions in case of unfavorable events during transportation under cold chain; verification of the pharmaceutical product condition and labels in the receiving area (required verifications to ensure that containers have not been opened); management of specific warehousing; labeling policy and others that include cleaning, alarm management, qualification of thermal equipment, qualification of transport system etc. [1]

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5.HPRA Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances (IA-G2020 3-0011)

6.Australian code of good wholesaling practice for medicines in schedule (Australian Government, Department of Health and Aged Care, Therapeutic Goods Administration, 2010)

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