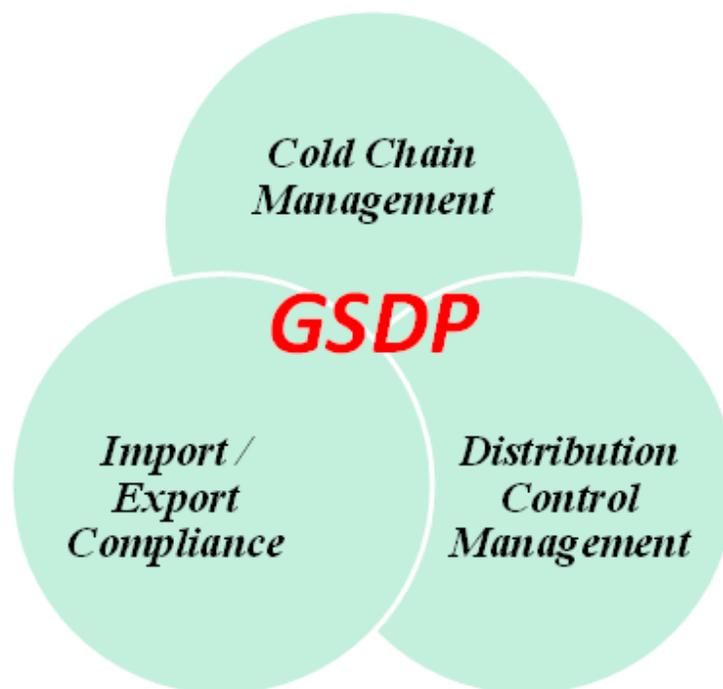




# Good Cold Chain Management for Temperature-Sensitive Pharmaceutical Products

*(Annex 1)*

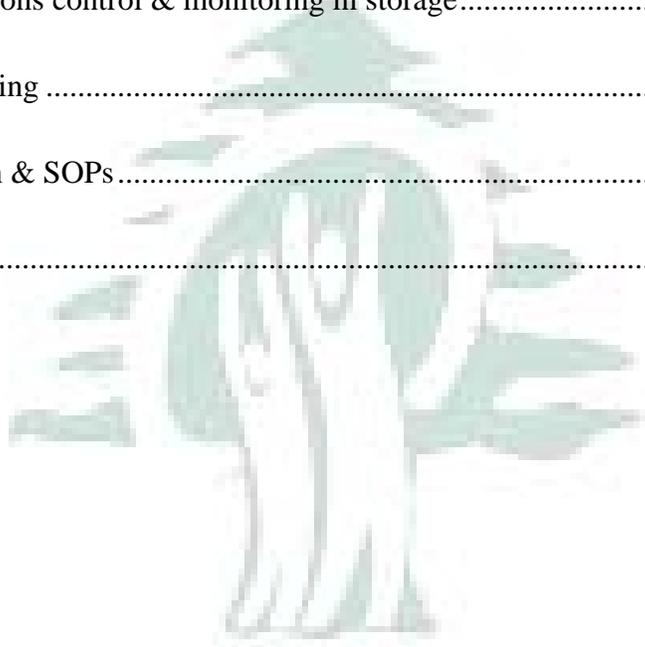


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## Introduction

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.

## Glossary

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

### **Storage temperature**

The temperature range listed on the TTSP label, and within the regulatory documentation, for long-term storage.<sup>[3]</sup>

### **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.<sup>[3]</sup>

### **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.<sup>[3]</sup>

### **Validation**

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

### **Temperature excursion**

An excursion event in which a TTSP 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.<sup>[3]</sup>

### **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.<sup>[3]</sup>

### **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.<sup>[3]</sup>

## 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. <sup>[1]</sup>

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. <sup>[1]</sup>

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 <sup>[1]</sup>

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 <sup>[1]</sup>

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

## 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. <sup>[1]</sup>
- 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. <sup>[1]</sup>
- 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. <sup>[1]</sup>
- 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. <sup>[1]</sup>
- 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). <sup>[1]</sup>
- 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. <sup>[1]</sup>

- 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).<sup>[1]</sup>
- 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.<sup>[1]</sup>
- 2.9 Loading activities (loading and unloading) should be done in a manner that preserves the quality of the drugs.<sup>[1]</sup>
- 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.<sup>[3]</sup>
- 2.11 Draw up procedures and memoranda of understanding to ensure that these shipments are cleared through customs as rapidly as possible.<sup>[3]</sup>
- 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.<sup>[1]</sup>
- 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.<sup>[1]</sup>

### 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.<sup>[3]</sup>

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.<sup>[3]</sup>

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<sup>[3]</sup>

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.<sup>[3]</sup>

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.<sup>[1]</sup>

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.<sup>[1]</sup>

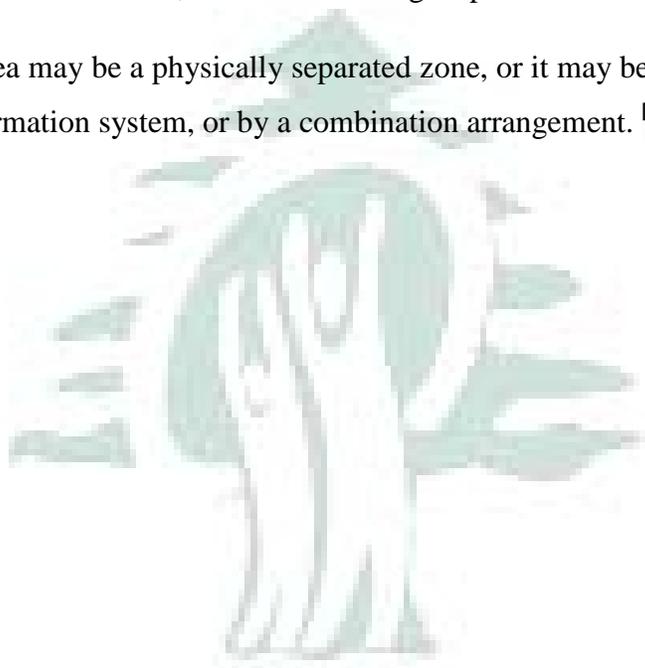
3.7 Drug distributors must maintain records and inventories that show receipt and distribution or "other disposition" of prescription drugs. These records must include the source of the drugs,

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. <sup>[1]</sup>

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. <sup>[3]</sup>



#### 4. Storage conditions control & monitoring in storage

##### *Temperature control*

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

4.2 Temperature control systems should comply with the following minimum requirements:

- System able continuously to maintain air temperatures within the set point limits throughout the validated storage volume
- Control sensors accurate to  $\pm 0.5$  °C or better
- Control sensors calibrated
- Control sensors located in areas where greatest variability in temperature is expected to occur in order to maximize available safe storage volume
- Control sensors positioned at the hot and cold spots determined by temperature mapping, even if affected by door opening, unless recommendations are being made not to store products in such areas
- Control sensors independent of the temperature monitoring system<sup>[3]</sup>

##### *Temperature monitoring*

4.3 The warehouse should provide air temperature monitoring systems and devices for all temperaturecontrolled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store temperature-sensitive products. <sup>[3]</sup>

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

- Monitoring sensors accurate to  $\pm 0.5$  °C or better for electronic devices and  $\pm 1$  °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<sup>[3]</sup>

#### 4.5 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<sup>[3]</sup>

#### 4.6 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.<sup>[1][2]</sup>

4.7 When specified on the label, controls for other storage conditions such as humidity, light, etc., should be in place. Storage areas should be designed or adapted to ensure good storage conditions. Adherence to these conditions should be checked, monitored and recorded.<sup>[1]</sup>

4.8 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.<sup>[3]</sup>

#### ***Humidity control and monitoring***

4.9 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  $\pm 5\%$  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<sup>[3]</sup>

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

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

#### ***Cleanliness of temperature-controlled stores***

4.12 The warehouse should implement a cleaning and decontamination program for all temperaturecontrolled 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<sup>[3]</sup>

#### ***Refrigeration equipment maintenance***

4.13 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 temperaturecontrolling equipment.
- Make arrangements to ensure that emergency maintenance is carried out within a time period that does not place temperature-sensitive productsat 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<sup>[3]</sup>

#### ***Calibration of temperature control and monitoring devices***

4.14 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. <sup>[3]</sup>

#### ***Calibration of humidity control and monitoring devices***

4.15 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. <sup>[3]</sup>

#### ***Alarm equipment verification***

4.16 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. <sup>[3]</sup>

4.17 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). <sup>[3]</sup>

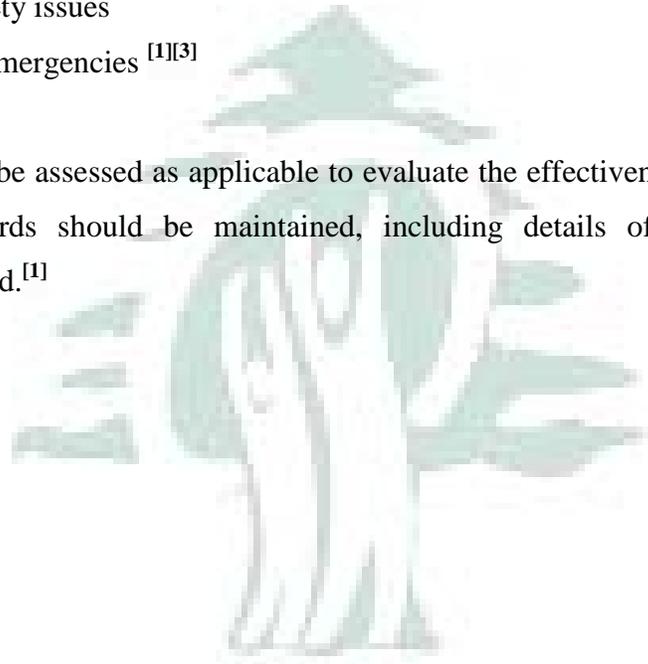
## 5. Personnel training

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. <sup>[1]</sup>

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 <sup>[1][3]</sup>

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. <sup>[1]</sup>



## 6. Documentation & SOPs

- 6.1 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.<sup>[1]</sup>
- 6.2 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.<sup>[1]</sup>
- 6.3 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.<sup>[1]</sup>
- 6.4 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.<sup>[1]</sup>
- 6.5 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.<sup>[1]</sup>

## References

1. Guide 069, Guidelines for temperature Control of Drug Products during Storage and Transportation
2. US Pharmaceopaedia: Chapter <1079>: « Good Storage & Shipping Practices »; Updates: « Good Storage and Transportation Practices for Drug Products » (2010)
3. WHO, Annex 9, Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO technical report series, No. 961, 2011)

