



الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Guidance for the Storage and Transport of Time- and Temperature–Sensitive Pharmaceutical Products

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Guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

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Abbreviations

CAPA	Corrective and preventive action (procedures)
DCVMN	Developing Countries Vaccine Manufacturers Network
FEFO	First to expire-first-out
FIFO	First-in-first-out
GDP	Good distribution practice
GMP	Good manufacturing practice
GPS	Global positioning system
GSP	Good storage practice
HVAC	Heating ventilating and air-conditioning (system)
IATA	International Air Transport Association
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IQ	Installation qualification
PCCIG	Pharmaceutical Cold Chain Interest Group
PDA	Parenteral Drug Association
SFDA	Saudi Food and Drug Authority
SKU	stock-keeping unit
SLA	Service level agreement
SMS	Short message service
SOP	Standard operating procedure
TTSP	Time- and temperature-sensitive pharmaceutical product
UPS	Uninterrupted power supply
USP	United States Pharmacopeia

Background

These guidelines set out the principal requirements for the safe storage and distribution of time- and temperature-sensitive pharmaceutical products (TTSPPs). They are based upon existing regulations and best practice guidance from a wide range of international sources (see References).

This guideline is adapted mainly from WHO “Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products”. The document is designed to give a balanced overview of the major aspects of good storage and distribution practice for TTSPPs. As such it deliberately includes references to requirements which can be found in SFDA guides to good manufacturing practice (GMP), WHO good storage practice (GSP) and good distribution practice (GDP). The purpose is not to supplant these source materials, but to ensure that the reader is aware of the relevant GMP, GSP and GDP implications when seen from the particular and specialized perspective of TTSPP management.

Glossary

The definition given below apply to the terms used in these guidelines.

They may have different meanings in other contexts.

Active systems

Actively powered systems using electricity or other fuel source to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulation (e.g. cold rooms, refrigerators, temperature-controlled trucks, refrigerated ocean and air containers).

Change control

The processes and procedures to manage system changes.

Common carrier

A seller of distribution services.

Controlled or hazardous time- and temperature-sensitive pharmaceutical products (TTSPPs) with high illicit value

Poisons, narcotics, psychotropic products, inflammable or explosive substances and radioactive materials.

Dunnage

Loose packing material used to protect TTSPPs from damage during transport.

External distribution

Transport of TTSPPs through various steps in the customer's supply chain (i.e. transport from a pharmaceutical manufacturer's distribution centre to commercial customers (including wholesalers, retailers and buying groups), to

clinical facilities or direct to the patient).

Installation qualification

The process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specifications and that it functions within predetermined limits when operated in accordance with the operating instructions.

Internal distribution

Transport of a TTSP within a pharmaceutical manufacturer's internal supply chain (i.e. all internal transports from manufacturing facility to packaging facility to warehouse to distribution centre).

Net storage capacity

The total volume available for storing TTSPs, taking account of the type of load support system employed (floor-standing pallets, adjustable pallet racking or shelving units), as modified by the utilization factor that can be achieved in the store.

Passive systems

Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of pre-conditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others.

Pests

Includes birds, bats, rodents and insects whose uncontrolled presence affects hygiene and cleanliness

Pharmaceutical product:

Substance or group of Substance used for treatment or prevention of diseases to humans, animals or given to correct or restore or modify physiological functions through the pharmacological effect or immune or metabolic action, or for medical diagnosis

Refrigeration equipment

The term “refrigeration” or “refrigeration equipment” means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

Service level agreement (SLA)

A service level agreement or contract is a negotiated agreement between the customers and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees and communication mechanisms. It can either be legally binding, or an information agreement. The SLA may also specify the target and minimum level performance, operation or other service attributes.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.

Storage temperature

The temperature range listed on the TTSP label, and within the regulatory documentation, for long-term storage.

Storage unit temperature/humidity distribution

The range and pattern of temperatures and/or humidity within a temperature-controlled storage unit during normal operation.

Suspect product

A TTSP where presentation and/or pharmacological formulation indicates that it has not been manufactured by the company named on the packaging. A TTSP that shows visible or pharmacological evidence of tampering.

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.

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.

Temperature-modified

Includes any environment in which the temperature is predictably maintained at a level different from that of the surrounding environment, (temperature below 25°C).

Time- and temperature-sensitive pharmaceutical product (TTSP)

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.

Transport temperature profile

Anticipated ambient temperature variation and duration to which a TTSP may be exposed during transport.

Utilization factor

The percentage of the total volume available for storing TTSPs that can reliably be achieved in practice, taking account of the types of stock-keeping unit (SKU), the types of load support system and the stock management systems used in the store.

1 Importation

1.1 Port Handling and Customs Clearance

1.1.1 *Port of Entry*

Import TTSPPs through a port of entry that is equipped to handle such products. Where this is not possible, ensure that arrangements are in place to provide the necessary level of protection and security.

Main reason: To minimize the risk of damage.

1.1.2 *Offloading*

As soon as possible after arrival, remove TTSPP shipments from the wharf or airport apron to a safe and suitable temperature-controlled storage location.

Main reason: To loss or avoid exposure to adverse ambient conditions.

1.1.3 *Temporary Storage at Port of Entry*

Store TTSPP shipments in a secure warehouse under the conditions recommended by the product manufacturer, until the shipment has been authorized for removal by customs.

Main reason: To loss or avoid damage during temporary storage.

1.1.4 *Customs Clearance*

Draw up procedures and memoranda of understanding to ensure that TTSPP shipments are cleared through customs as rapidly as possible. This can be facilitated by a pre-clearance procedure carried out by the SFDA, clearing agent or freight forwarder in collaboration with customs.

Main reason: To avoid delays during customs clearance that may cause temperature excursions and place TTSPPs at risk.

2 Storage Buildings

2.1 Construction Standards

Construct or procure storage buildings that are:

- Purpose-designed for the storage of TTSPPs, or well-adapted for this purpose;
- Designed to suit the prevailing climate, making maximum use of passive heating, cooling and ventilation;
- Designed and equipped to minimize the consumption of electricity and other fuel sources;
- Constructed using materials and finishes that are robust, easy to clean and which are selected to minimize long-term maintenance.
- Built to minimize hiding and nesting places for pests.

Reasons: Storage in unsuitable and poorly designed buildings places TTSPPs at risk. Buildings constructed using inappropriate materials and technologies are difficult to operate and maintain in resource-constrained settings.

2.2 Accommodation and Layout

Ensure that the storage buildings are well laid out and contain all the necessary storage areas, goods assembly, receiving and dispatch bays and office accommodation needed for efficient operation of the TTSP store.

2.3 Loading and Receiving Bays

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, wind and from extremes of heat, cold and solar radiation that could damage TTSPPs, and measures are taken to minimize pest activity in these areas. Provide receiving areas with suitable equipment to clean reusable transport containers after their contents have been unloaded, and before the containers are stored for re-use.

Main reason: maintenance of product quality and Protection against contamination of TTSPPs.

2.4 Goods Assembly and Quarantine Areas

2.4.1 Goods assembly areas

Provide sufficient space to receive, assemble and pack TTSPPs for dispatch under temperature-controlled conditions (below 25C for no longer than two hours apply to product stored from 2-8°C assuming that such condition is covered by the product stability test) . Preferably, these areas should be physically close to the (2-8°C) temperature-controlled storage area.

Main reason: Protection of TTSPPs during arrival, order assembly and dispatch.

2.4.2 Holding Area for Incoming Goods

Provide a temperature-controlled holding area for incoming TTSPPs pending their acceptance into the main storage area. The holding area may be a physically separated zone, or it may be defined using a suitable stock control information system, or by a combination arrangement. Where goods are conditionally released to be held in the warehouse, awaiting clearance, they must be physically separated and secured.

Main reason: Incoming items may need inspection and/or regulatory clearance, including laboratory testing.

2.4.3 Quarantine Area

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.

Main reason: Items for re-stocking, testing and disposal should be kept separate to avoid the risk of inappropriate use.

2.5 Environmental Control of Ancillary Areas

Ensure, that ancillary areas where TTSPPs are temporarily held during arrival, order assembly or dispatch are:

- Maintained within the temperature range specified for the goods being handled;
- Maintained within the humidity range specified for goods that are adversely affected by extreme condition of relative humidity and are not sufficiently protected by their packaging;
- Protected from undue exposure to direct sunlight and extreme weather condition .
- Protected against dust, dirt and waste accumulation.
- Adequately ventilated.
- Adequately lit to enable operations to be carried out accurately and safely.
- Controlled and monitored during the times when TTSPPs are handled; (see 3.5.1-3.5.2).

Main reason: Protection of TTSPP quality during arrival, order assembly or dispatch.

2.6 Power Supply

2.6.1 Uninterrupted Power Supply

Ensure that all temperature- controlling equipment for TTSPP storage (i.e. refrigerators, freezers, cold storage areas and alarms) and all monitoring system are connected to an uninterrupted power supply (UPS) system. In addition, where necessary, other equipment / system have to be connected (UPS) (i.e building management systems, heating, ventilation and air-conditioning (HVAC) systems, compressors, air-handling units and related

computer equipment). Where a generator and associated control equipment is used it should:

- Be able to manage the combined start-up load of all connected temperature-controlling and temperature-monitoring equipment.
- Not exceed the defined parameters of the main power supply;
- Be equipped with automatic main failure start-up and automatic shutdown when power is restored; and
- Have adequate fuel tank capacity and sufficient fuel to cover a prolonged power outage.
- Regularly test and service UPS equipment and generators. Maintain records to demonstrate compliance.

Main reason: Loss prevention.

2.7 Building maintenance

Implement a planned preventive maintenance programme to ensure that storage buildings and building utilities are well maintained. Keep records to demonstrate compliance with the programme.

Main reason: To ensure that storage buildings continue to protect stored products against damage.

3 Temperature-Controlled Storage

3.1 Storage Capacity of Temperature-Controlled Stores

Ensure that the net storage capacity of the temperature-controlled stores is sufficient to accommodate peak TTSPS stock levels and their associated transit temperature protection components (i.e. freezer blocks, flexible ice blankets, refrigerated gel packs, phase change materials and insulated packaging, if retained), under correct temperature conditions and in a manner which enables efficient and correct stock management operations to take place.

Main reason: To avoid the risks associated with overstocking and to ensure that good warehousing practices can be adopted (i.e. first in-first out (FIFO) or earliest expiry-first out (FEFO)). Overstocking makes FIFO or FEFO handling difficult or impossible and hinders accurate physical stock counts.

3.2 Temperature-Controlled Storage

Ensure that TTSPS are stored in temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers which comply with the following requirements.

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

- Capable of maintaining the temperature range defined by the system set points over the full annual ambient temperature range experienced at the store location;
- Equipped with an auto-defrost circuit which has a minimal effect on temperature within the unit during the defrost cycle and maintains temperature within specification for this period;
- Equipped with a low temperature protection circuit in cold climates where there is a risk of breaching the low temperature set point for TTSPS that are damaged by exposure to low temperatures;
- Connected to a UPS as described in
- Equipped with a calibrated continuous temperature monitoring system with sensors located at points representing greatest temperature

variability and temperature extremes;

- Equipped with continuous humidity monitoring devices with sensors located at points representing humidity extremes;
- Equipped with alarms to indicate temperature excursions and/or refrigeration failure;
- fitted with lockable doors, or an access control system, as necessary; locks must have a safety device so that doors can be freely opened from the inside; and qualified as defined in clause 3.6

Refrigerators and freezers should be:

- Purpose-designed for the storage of TTSPPs• capable of maintaining the temperature range specified by the TTSPP manufacturer over the full annual ambient temperature range experienced at the storage site.
- Equipped with calibrated temperature monitoring devices appropriate to the level of risk but preferably capable of continuous recording and with sensor(s) located at a point or points within the cabinet which most accurately represents the temperature profile of the equipment during normal operation.
- Preferably equipped with alarms to indicate temperature excursions or refrigeration failure.
- fitted with lockable doors or lids, or access control system, as necessary; and qualified and/or tested as defined in clause 3.6

Main reason: To maintain labeled TTSPP storage temperatures during long- term storage.

3.3 Temperature-Controlled Storage for Controlled and Hazardous Products

Ensure that controlled and hazardous TTSPPs are securely stored:

- Provide dedicated temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers for these TTSPPs, in separate secure areas.

Main reason: To protect this category of TTSPPs against theft and misuse

and to safeguard workers and general storage areas in the event of an accident involving hazardous substances.

3.4 Temperature and humidity control and monitoring in storage

3.4.1 *Temperature Control*

Provide thermostatic temperature control systems for all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPPs. 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 ± 0.5 °C or better.
- Control sensors calibrated as described in clause 3.9.1.
- 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.

3.4.2 *Temperature monitoring*

Provide air temperature monitoring systems and devices for all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPPs. Comply with the following minimum requirements:

General requirements

- Monitoring sensors accurate to ± 0.5 °C or better for electronic devices.
- Monitoring sensors calibrated as described in clause 3.9.1.
- Monitoring sensors located in areas where greatest variability in temperature is expected to occur within the qualified and/or tested storage volume as defined in clause 3.6.
- 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.

Temperature-controlled rooms, cold rooms and freezer rooms

- 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 during unforeseen event.

Refrigerators and freezers

- Ensure 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.
- Provide documentation for each appliance which can be stored and accessed.

Main reason: To maintain labeled TTSP temperatures during long-term storage.

3.4.3 Humidity Control

Provide humidity control in temperature-controlled rooms that are used to store TTSPs which are adversely affected by high or low relative humidity. Such products are typically labeled “store in a dry place”, or carry similar wording and require a humidity-controlled environment.

3.4.4 Humidity Monitoring

Provide humidity monitoring systems and devices in temperature-controlled rooms that are used to store TTSPs which require a humidity-controlled environment. Comply with the following minimum requirements:

- sensors accurate to $\pm 5\%$ RH;

- sensors calibrated as per clause 3.9.2
- sensors located to monitor worst-case humidity levels within the qualified storage volume defined in clause 3.6
- sensors positioned so as to be minimally affected by transient events such as door opening.
- provides a humidity record with a minimum recording frequency of six times per hour for each sensor position;
- provides documentation for each sensor position which can be stored and accessed; and
- continues to operate independently in the event of a power failure during unforeseen event.

Main reason: To maintain labeled TTSPH humidity conditions during long-term storage.

3.5 Alarm Systems

3.5.1 *Temperature Alarms*

Provide temperature alarm systems for temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPHs. The temperature alarm systems should Comply with the following minimum requirements:

- Sensors accurate to ± 0.5 °C.
- Sensors calibrated as described in clause 3.9.1
- Sensors located to monitor worst-case temperatures within the validated storage volume defined in clause 3.6, where the alarm system is not integrated with the temperature monitoring system, sensors should be located close to the temperature monitoring sensors.
- Sensors positioned so as to be minimally affected by transient events such as door opening.
- Preferably, there should be appropriately located visual alarm(s) in addition to the audible alarm(s).
- Preferably there should be an automatic telephone dial-up or SMS text warning system to alert on-call personnel when an alarm is

triggered outside working hours.

Main reason: Loss prevention.

3.5.2 Humidity Alarms

Provide humidity alarm systems for temperature-controlled rooms used to store TTSPPs that require a humidity-controlled environment. Comply with the following minimum requirements:

- Sensors accurate to $\pm 5\%$ relative humidity (RH);
- Sensors calibrated as described in clause 3.9.2
- Sensors located to monitor worst-case humidity levels within the validated storage volume defined in clause 3.6, where the alarm system is not integrated with the humidity monitoring system, sensors should be located close to the humidity monitoring sensors;
- Sensors positioned so as to be minimally affected by transient events such as door opening
- Preferably, there should be appropriately located visual alarm(s) in addition to the audible alarm(s).
- Preferably there should be an automatic telephone dial-up or SMS text warning system to alert on-call personnel when an alarm is triggered outside working hours.

Main reason: Loss prevention.

3.6 Qualification of temperature-controlled stores

Qualify new temperature-controlled storage areas and new refrigeration equipment before it becomes operational. The qualification procedure should:

- demonstrate the air temperature profile throughout the storage area or equipment cabinet, when empty and in a normal loaded condition;
- Define zones which should not be used for storage of TTSPPs (for example areas in close proximity to cooling coils, cold air streams or heat sources).
- Demonstrate the time taken for temperatures to exceed the designated limits in the event of power failure.

Fully document the initial qualification. Carry out additional qualification

exercises whenever modifications are made to the storage area that may increase loading or affect air circulation, or when changes are made to the refrigeration equipment, such as a change in the set point. Consider the need for requalification whenever temperature and/or humidity monitoring shows unexplained variability that is greater than normal.

Qualification may not be required for equipment which requires little or no site assembly or commissioning, such as vaccine refrigerators and freezers that have been independently tested and found suitable for the storage of TTSPPs. Independent testing must be carried out between the chosen set points and under the ambient temperature conditions at different session to which the equipment will be exposed during operation.

Main reason: To ensure that labeled TTSPP temperatures can be maintained during long-term storage.

3.7 Cleanliness of Temperature-Controlled Stores

Implement a cleaning and decontamination program for all temperature-controlled rooms:

- Ensure that floor areas are fully accessible for cleaning. Do not store goods directly on the floor.
- Do not permit storage of any non-pharmaceutical products except transport-related items such as icepacks, gel packs and the like.
- Do not allow the accumulation of dust, dirt and waste, including packaging waste.
- Take precautions against spillage or breakage, and cross-contamination.
- Do not allow accumulation of frost and ice, particularly ice contaminated by spillages.
- Collect waste in designated closed containers and arrange for safe disposal at frequent intervals.

Maintain cleaning records to demonstrate compliance.

Main reason: Protection against damage and contamination of TTSPPs

and hazards to workers, arising from spillage or breakage.

3.8 Refrigeration Equipment Maintenance

Implement a maintenance programme 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 TTSPPs at risk of damage.
- Ensure that there is a contingency plan to move products stored in non-functioning 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.

Main reason: Loss prevention.

3.9 Calibration and Verification of Control and Monitoring Devices

3.9.1 *Calibration of Temperature Control and Monitoring Devices*

Calibrate devices against a certified, traceable reference standard at least once a year. 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.

3.9.2 *Calibration of humidity control and monitoring devices*

Calibrate devices against a certified, traceable reference standard at least once a year. Single-use devices that are supplied with a manufacturer's calibration certificate do not need to be re-calibrated.

3.9.3 *Alarm equipment verification*

Check functionality of temperature and humidity alarms at least once every six months at the designated set points.

Maintain records to demonstrate compliance.

Reason: To ensure that labeled TTSP storage temperatures and humidity control can be maintained during long-term storage.

4 Materials Handling

4.1 Materials Handling Equipment

Where powered materials handling equipment is used in temperature-controlled rooms, cold rooms or freezer rooms, select equipment which is certified for safe use in confined spaces.

Reason: Protection of the workforce.

5 Transport and Delivery

5.1 Product Stability Profiles

Transport TTSPs in such a manner that transport temperatures meet the product storage requirements (so that temperature excursions above or below the manufacturer's labeled storage temperature range do not adversely affect product quality). Product stability data must demonstrate the acceptable temperature excursion time during transport.

Reason: Protection of TTSPs against degradation.

5.2 Transport Route Profiling and Qualification

Profile and qualify transport routes:

- Select the most suitable methods for protecting TTSPs against anticipated ambient temperature and humidity conditions throughout the year.
- Use suitable methods, including published standards, weather data, laboratory tests and field tests to select suitable transport equipment and shipping containers.

Main reason: To ensure that TTSPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

5.3 Temperature-Controlled Transport

5.3.1 *Air transport*

Ensure that any carrier contracted to transport TTSPs operates under the terms of a formal service level agreement (SLA) drawn up between the parties. The carrier is to be made responsible for maintaining load temperatures within the transport temperature profile defined for each product.

Main reason: To ensure that the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product.

5.3.2 *Temperature-controlled road vehicles operated by common carriers*

Temperature control in vehicles operated by a common carrier must be

qualified and the details and responsibilities for this process should be set out in a formal SLA drawn up between the parties.

Main reason: To ensure that the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product.

5.3.3 Temperature-controlled road vehicles generally

Ensure that temperature-controlled road vehicles used for the transport of TTSPPs are equipped with calibrated temperature monitoring devices with sensors located at points representing worst-case temperature.

Moreover, such vehicles are supposed to be:

- Capable of maintaining the temperature range defined by the system set points over the full annual ambient temperature range experienced over known distribution routes and when the vehicle is in motion, or parked with the main engine stopped;
- Equipped with a low temperature protection circuit in cold climates where there is a risk of breaching the low temperature set point for TTSPPs that are damaged by exposure to low temperatures;
- Equipped with alarms to alert the driver in the event of temperature excursions and/or refrigeration unit failure;
- Fitted with doors with security seals and/or security locks that protect against unauthorized access during transit;
- Equipped with humidity monitoring systems and devices for transport TTSPPs that required a humidity-controlled environment. Sensors accurate to ± 0.5 °C and $\pm 5\%$ RH for temperature and humidity respectively.
- Equipped with temperature (and if applicable humidity) recording system with a minimum recording frequency of six times per hour for each sensor position; and documentation which can be stored and accessed.

Note: the temperature and humidity monitoring systems should have a minimum recording frequency of six times per hour for each

sensor position.

- Qualified as defined in clause 5.5
- Regularly calibrated and maintained and records kept to demonstrate compliance.

Main reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product.

5.4 Temperature Monitoring in Passive and Active Shipping Containers

Use electronic loggers and/or other suitable indicators to monitor temperature and/or humidity exposure during distribution. Monitor and document indicator status upon arrival.

Main reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product. and that compliance can be demonstrated to SFDA.

5.5 Qualification of Temperature-Controlled Road Vehicles

The qualification procedure should:

- Demonstrate that the air temperature distribution is maintained within the limits specified throughout the temperature-controlled compartment for both air and product temperatures for commonly used load layouts and at the ambient temperature extremes anticipated during normal operation over known routes;
- Demonstrate the humidity distribution throughout the temperature-controlled compartment for commonly used load layouts, where products are being transported that require a humidity-controlled environment;
- Define zones within the vehicle's payload area which should not be packed with TTSPPs (for example areas in close proximity to cooling coils or cold air streams).
- Demonstrate the time taken for temperatures to exceed the designated maximum in the event that the temperature-controlling unit fails.
- Document the qualification exercise.

An alternative approach is to perform an initial full qualification on each trailer/refrigeration unit type combined with an installation qualification (IQ) for example when a new vehicle becomes operational.

Carry out additional qualification exercises whenever significant modifications are made to the vehicle or whenever temperature and/or humidity monitoring shows unexplained variability that is greater than normal.

Main reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to SFDA.

5.6 Calibration and Verification of Transport Monitoring Devices

5.6.1 *Calibration of transport temperature control devices*

Calibrate devices against a certified, traceable reference standard at least once a year.

5.6.2 *Calibration of transport temperature monitoring devices*

Calibrate devices against a certified, traceable reference standard at least once a year.

5.6.3 *Calibration of transport humidity monitoring devices*

Calibrate devices against a certified, traceable, reference standard at least once a year.

5.6.4 *Verification of transport alarm equipment*

Check functionality of temperature and humidity alarms at the designated set points. Check functionality of security alarm systems. Carry out these checks at least once a year.

Maintain records to demonstrate compliance.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to SFDA.

5.7 Shipping Containers

5.7.1 *Container selection generally*

Select shipping containers that:

- Comply with applicable national and international standards relevant to the product type and the chosen transport route and mode(s);
- Protect personnel and the general public from hazards arising from spillage, leakage or excessive internal pressure;
- Protect the product being transported against mechanical damage and the anticipated ambient temperature range that will be encountered in transit; and
- Can be closed in a manner that allows the recipient of the consignment to establish that the product has not been tampered with during transport.

Main reason: Quality assurance and safety.

5.7.2 *Uninsulated containers*

Ensure that uninsulated containers are correctly used, in a manner which protects their contents:

- Transport uninsulated containers in a qualified temperature-controlled environment such as an actively or passively temperature-controlled vehicle;
- Ensure that the transport system is able to maintain the temperature of the TTSP within the product's storage conditions as stated by the product manufacturer.

Main reason: Quality assurance and safety.

5.7.3 *Qualification of insulated passive containers*

Qualify insulated passive containers, including any and all necessary ancillary packaging such as temperature stabilizing medium, dry ice, ice or gel packs, cool water packs or warm packs, phase change materials, partitions, bubble wrap and dunnage:

- Ensure that the qualified packaging system is capable of maintaining the TTSP within the storage conditions as stated by the product manufacturer. Container qualification should include full details of the packaging assembly, the thermal conditioning regime and the

minimum and maximum shipping volume, weight and thermal mass that can safely be accommodated in the container. Qualification should also include the correct placement of temperature monitors where these are used;

- Take account of the transport route and of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of arrival in the recipient's temperature-controlled store.

Main reason: To ensure that TTSPPs can safely be transported within the transport temperature profile defined for each product and that compliance can be demonstrated to SFDA.

5.7.4 Qualification of active containers

Qualify active containers:

- Ensure that the container is capable of maintaining the TTSPP within the storage condition as stated by the product manufacturer;
- Take account of the transport route and of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of arrival in the recipient's temperature- controlled store.

Main reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to SFDA.

5.8 Shipping Container Packing

Pack TTSPP shipping containers to:

- Comply the exact specified configuration to ensure that the correct TTSPP temperature range is maintained.
- Minimize the risk of theft and fraud and assure the recipient that the goods have not been tampered with while in transit, for example by using locked containers or shrink-wrapped pallets.
- Minimize the risk of mechanical damage during transport.
- Protect freeze-sensitive products against temperatures below 0 °C

when frozen packs are used;

- Protect products against light, moisture and microorganisms contamination.
- Protect products against adverse effects when dry ice is used as a coolant.
- Clearly label containers to identify the correct transport temperature range and to show correct orientation for handling.
- Ensure that packages containing dangerous goods (including dry ice) are labeled in compliance with relevant transport regulations and requirements.

Main reason: To ensure that shipping containers are systematically used in the manner defined during the container qualification process and that this can be demonstrated to SFDA.

5.9 Product Handling During Packing and Transport

Handle TTSPPs correctly during packing and transport:

- Pack TTSPPs in an area set aside for the assembly and packaging of these products as specified in clause 2.6
- Take precautions against spillage or breakage, contamination and cross-contamination;
- Deliver TTSPPs to outside recipients by the most suitable mode(s) of transport available in order to minimize delivery time; and
- Ensure that patients receiving TTSPP deliveries are given clear advice on correct storage of the product before use.

Main reason: To maintain TTSPP quality during transport.

5.10 Cleaning Road Vehicles and Transport Containers

Implement a cleaning and decontamination programme for all road vehicles and reusable shipping containers used to transport TTSPPs:

- Ensure that all internal surfaces of load compartments are regularly cleaned;
- Do not allow the accumulation of dust, dirt and waste, including packaging waste in load compartments, or in reusable shipping

containers

- Take precautions against spillage or breakage, and cross-contamination;
- Do not allow accumulation of frost and ice in refrigerated vehicles, particularly ice contaminated by spillages; and
- Collect waste in designated closed containers and arrange for safe disposal at frequent intervals.

Maintain cleaning records for vehicles and reusable shipping containers to demonstrate compliance.

Main reason: Protection against damage and contamination of TTSPPs and hazards to workers arising from spillage or breakage.

5.11 Transport of returned and recalled TTSPPs

5.11.1 Transport of returned TTSPPs

Ensure that the returned TTSPPs are transported under the same conditions as those used for the initial delivery:

- The sender and recipient must work together so that the product is maintained within the temperature range needed to meet the manufacturer's stated product labeled storage conditions.
- Take account of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of return; and
- Quarantine returned TTSPPs in temperature-controlled storage pending a decision by the quality control department or qualified person to dispose of the product or to return it to stock.

Main reason: To ensure that returned and recalled TTSPPs are maintained within the correct transport temperature profile so that they can safely be restocked if a decision to do so is made.

5.11.2 Transport of recalled TTSPPs

Ensure that recalled TTSPPs are:

- Marked for disposal as either "recalled" or "withdrawn";
- Transported back from the recipient and quarantined under secure

conditions pending a final decision on disposal.

6 Labeling

6.1 Labeling Generally

Label internal shipping and external distribution containers containing TTSPPs as follows:

- Identify the product in accordance with all national and international labelling requirements relevant to the container content, transport route and mode(s);
- Identify hazardous products in accordance with relevant national and international labelling conventions; and
- Indicate the appropriate temperature and humidity ranges within which the product is to be transported and/or stored.

6.2 Labeling Air-Freighted Shipments

In cases are TTSPPs to be air-freighted, the package(s) should be labeled using the standard International Air Transport Association (IATA) time and temperature-sensitive symbol. Apply the label to the outer surface of individual shipping packages, overpacks or bulk containers.

Main reason: To ensure that products are correctly and safely handled at all points in the supply chain.

7 Stock Management

7.1 Incoming Goods

7.1.1 *Product arrival checks*

Check and record the following for all incoming TTSPPs:

- Product name, item code (identifier), strength, and batch/lot number
- Quantity received against order
- Name and address of the supplying site
- Examine containers for tampering, damage or contamination;
- Examine expiry dates accept short-dated products only if prior agreement has been reached with the supplier and reasonably justified. do not accept products that have expired or which are so close to their expiry date that this date is likely to occur before use by the consumer.
- Delays encountered during transport.
- Status of any attached temperature recording device(s) and/or time/
- Temperature indicators.
- Verify that required storage and transport conditions have been maintained.

7.1.2 *Actions following arrival checks*

- Enter product details, including product name/number, strength, batch numbers, quantities received, expiry dates and acceptance status into the stock recording system.
- Store checked goods under the correct temperature and security regime immediately upon receipt.
- Quarantine defective or potentially defective products, products with incomplete or missing paperwork, products that experienced unacceptable temperature excursions during transport, or products suspected to be counterfeit. Do not release until checks have been completed satisfactorily.
- Any deviation from the approved storage condition must be reported to SFDA, which will determine the product disposition.

- Report any defects to SFDA and the supplying store or holder of the marketing authorization
- Do not transfer to saleable stock until all relevant disposition procedures have been completed.

Main reason: To ensure that incoming TTSPPs are in acceptable condition, accurately recorded and correctly stored and that defective and/or incorrect shipments are followed up with the supplier.

7.2 Outgoing Goods (External Deliveries)

7.2.1 Management of outgoing goods

Implement outgoing goods procedures to ensure that:

- Transport vehicle conformity, including conformity with SLA or quality assurance (QA) agreements, is checked before loading goods.
- Expired products are never issued.
- Products with short expiry dates are not issued unless the recipient accepts that they can be consumed before the expiry date is reached.
- Products are distributed in strict FEFO order unless a product-based time-temperature exposure indicator, such as a vaccine vial monitor, demonstrates that a batch should be distributed ahead of its FEFO order.
- Details of any temperature monitoring devices packed with the external distributions are recorded.
- Details of outgoing products, including product name/number, strength, batch numbers, expiry dates and quantities distributed, are entered into the stock recording system.

7.2.2 Actions following dispatch

Monitor TTSPPs following dispatch in order to:

- Trace products to their intended destination;
- Record and retain records to provide assurance of goods arrival status.
(Attach annex 1)
- Take appropriate action in the event of returns, recalls or complaints.

Main reason: To ensure that outgoing TTSPPs are in acceptable condition,

that short-dated stock does not accumulate in the store and that evidence is kept to demonstrate that correct quantities are distributed and received in good condition.

7.3 Product Return, Recall, Withdrawal and Disposal Procedures

7.3.1 *Return procedures*

Manage product returns as follows:

- Quarantine returned TTSPPs in a suitable temperature-controlled area and under the security conditions applicable to the product type.
- Do not return to saleable stock unless storage and transport temperature conditions after dispatch from the distribution site have been fully verified and documented, including the return leg to the distribution site.
- Where appropriate, obtain written advice from the holder of the marketing authorization regarding handling and/or disposal of the returned TTSPP.
- If returned stock is re-issued, distribute in FEFO order or in accordance with the exposure status of any product-mounted time-temperature indicator device.
- Quarantine returned TTSPPs that have been exposed to unacceptable storage and/or transport temperatures and mark for disposal.
- Maintain records of all returned TTSPPs.

Main reason: Protection of the public.

7.3.2 *Recall procedures*

Manage product recalls as follows:

- Conduct urgent and non-urgent TTSPP recalls in accordance with an agreed emergency plan.
- Notify SFDA
- Notify all affected customers as applicable.
- Quarantine any remaining inventory of recalled TTSPPs and mark for further investigation before disposal.
- Maintain records of all TTSPP recalls, including reconciliation of

quantity sold, quantity returned, quantity remaining or quantity consumed.

Main reason: Protection of the public.

7.4 Traceability or stock tracking

Stock and distribution records should enable traceability, or stock tracking, of TTSPPs from the point of supply to the end-user or patient.

Traceability should include records of the temperature exposure of the product during internal shipping and storage. These records should include:

- For incoming goods: status of shipping indicators used, status of product-based time-temperature indicators and physical condition of goods and time of receipt.
- For outgoing goods: type of shipping indicators used, status of product-based time-temperature indicators and physical condition of goods and time of dispatch.
- Monitor, record, and investigate discrepancies.

Main reason: To demonstrate that TTSPPs have been correctly distributed and to facilitate product recalls and detect theft and fraud.

8 General Procedures and Record-Keeping

8.1 Emergencies and Contingency Planning

Make contingency arrangements for the safe storage of TTSPPs in the event of emergencies, including, but not confined to:

- Extended power supply outages equipment failure; and vehicle breakdown during transport of TTSPPs.
- Prepare action plans to deal with products subjected to temperature excursions to guaranty that such condition do not effect product negatively.
- Ensure that the responsible staff know, and have rehearsed, the appropriate actions to be taken in the event of the identified emergency scenarios.

Main reason: Loss prevention.

8.2 General Record-Keeping

8.2.1 Record-keeping

Maintain comprehensive records and ensure that they are laid out in an orderly fashion and are easy to check.

Paper records must be:

- Stored and maintained so that they are accessible and easily retrievable.
- Labeled, dated and filed for easy identification.
- Protected against deterioration and loss due to fire, flood or other hazards.
- Kept secure and protected against unauthorized access.
- Signed and dated by authorized persons and not changed without due authorization.

Computer records must be:

- Logically filed for easy identification and retrieval.
- Kept secure and protected against unauthorized access.
- Where feasible, manually signed, dated and scanned or when

electronically archived dated, encrypted and with check-sum.

- Regularly backed-up and archived on media that are independent of the record-keeping computer system(s). Back-up media may be a separate secure server, a separate hard disc, a flash drive or other digital media appropriate to the scale of the operation.

8.2.2 Content of Records

Ensure that the following traceability data is recorded for each TTSP batch number, as applicable:

- Status of product on arrival.
- Temperature and humidity records including records of excursions outside labeled storage and/or transit temperature specification conditions.
- General TTSP stock transactions, including purchase and sale records.
- Stock tracking.
- Return, recall, withdrawal and disposal reports, where relevant.
- Product complaint reports, where relevant.
- Maintain all records for minimum one year after expiry date .

8.2.3 Record review and retention

Ensure that records are reviewed and approved on a regular basis by a designated quality person. Ensure that records are accessible for review by end-users and SFDA . Retain records for the minimum one year after expiry date.

Reason: Internal quality control, transparency and external inspection by SFDA and other interested parties.

8.3 Temperature and humidity records

8.3.1 Temperature records

Monitor and record storage temperatures in all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, as follows:

- Check and record temperatures at least twice daily — in the morning and evening — and preferably continuously.

- Review temperature records monthly and take action to rectify systematic excursions.
- Systematically file temperature records for each storage environment or piece of equipment to ensure traceability. Keep records for at least one year after the end of shelf-life of the stored material or product

8.3.2 Humidity records

When storing products which are adversely affected by extremely high or low relative humidity (see clause 3.4.3), monitor and record humidity levels in all temperature-controlled rooms as follows:

- Record humidity at least twice every 24 hours or preferably continuously.
- Check humidity records daily.
- Review humidity records monthly and take action to rectify systematic excursions.
- Systematically file humidity records for each temperature-controlled room to ensure traceability. Keep records for at least one year after the end of the shelf-life of the stored material or product.

Main reason: Internal quality assurance and availability of records for review by SFDA and other interested parties.