GUIDELINES FOR GOOD COLD CHAIN MANAGEMENT PRACTICES FOR TIME & TEMPERATURE-SENSITIVE DRUG PRODUCTS

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This draft guideline is uploaded on the official website of DRAP dated on 27th March, 2023, for seeking comments and suggestions from stakeholders on the draft document. Stakeholders can submit their comments and suggestions within 15 days of uploading this document using prescribed format, (further information on comments submission can access on this link. Comments and suggestions can be forwarded via email to ajmal.sohail@dra.gov.pk, copying at akbar.ali@dra.gov.pk, or can be posted at mailing address, Additional Director, Quality Assurance & Lab Testing, Drug Regulatory Authority of Pakistan, 3rd floor TF Complex, 7th Mauve Area, G-9/4, Islamabad.

Drug Regulatory Authority of Pakistan
Islamabad-Pakistan

1. HISTORY

This is the first edition of these guidelines.

2. APPLICATION - Guidelines for industry

This document will provide guidance to manufacturers, importers, exporters of drug products and their active pharmaceutical ingredients (APIs) / drug substances, including wholesalers, distributors, transporters and sale outlets for storage and distribution of time & temperature sensitive pharmaceuticals and biologicals to ensure that the quality and efficacy of the drug product will not be compromised.

These guidelines are also applicable on TTSDPs intended for use in clinical trials / investigational purposes, as well as on the physician samples.

These guidelines also assist hospitals / healthcare institutions, clinicians and healthcare providers in storage and distribution of time & temperatures sensitive drug products.

3. PURPOSE

The guidelines set out the principal requirements for the safe storage and distribution of time- and temperature-sensitive pharmaceutical products (TTSDPs). These guidelines emphasize the increased importance of pharmaceutical cold chain management as a result of changing product environment, the requirements for Good Storage and Distribution Practices, current regulatory trends, quality management, risk assessment factors, and temperature monitoring system.

The purpose of this document is to ensure that these products retain their quality throughout its storage and distribution in the supply chain. For this purpose, it is necessary to monitor compliance of the product with suitable quality specifications throughout the shelf life. And make sure that the conditions do not allow the risk exposure to temperatures outside of their recommended storage conditions.

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4. INTRODUCTION

The movement and storage of TTSDPs defines the supply chain as a time & temperature-controlled chain, since these products need constant maintenance of temperature so that the cold chain may not be broken to ensure that the product quality is not compromised. This requirement for a dependable cold chain allows safe and doubt free transport of drug till the end product user.

This document stresses the importance of adhering to it by all these entities 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 TTSDPs to the person dispensing or providing TTSDPs directly to a patient or consumer.

These guidelines should neither be taken as complete or definite interpretation of law nor does it replace or establish a formal decision of Authority.

These guidelines are derived from the Annex 9 WHO model guidance for the storage and transport of time- and temperature–sensitive pharmaceutical products (TRS No.961, 2011)

5. LEGAL REQUIREMENTS

Drug Regulatory Authority of Pakistan, under Section 7 (c) (ix) of DRAP Act, 2012 is mandated for implementation of internationally recognized standards such as good laboratory practices, current good manufacturing practices, good distribution practices, cold chain management in a systematic manner through adaptation of international recognized guidelines.

Registration holders of TTSDPs including manufacturers, Importers and exporters along with their authorized distributors, are required to provide suitable storage conditions throughout the life cycle of the product under the Drugs (Licensing, Registering & Advertising) Rules, 1976. Similarly, pharmacies, medical stores and other authorized sale outlets, and healthcare institutions are required to provide suitable storage and distribution while dispensing TTSDPs under relevant provincial drug sale rules as applicable.

6. DEFINITIONS AND ACRONYMS:

CAPA	corrective and preventive action (procedures)
DRAP	Drug Regulatory Authority of Pakistan
EEFO	earliest-expiry-first-out. Used in this document as equivalent to FEFO (first to expire-first-out)
FIFO	first-in-first-out
GDP	Good distribution practice
GMP	Good manufacturing practice
GSP	Good storage practice
HVAC	heating ventilating and air-conditioning (system)
IATA	International Air Transport Association
IQ	installation qualification
PCCIG	Pharmaceutical Cold Chain Interest Group
PDA	Parenteral Drug Association
SKU	stock-keeping unit
SLA	service level agreement
SMS	short message service
SOP	Standard operating procedure
TTSDP	time - and temperature-sensitive drug product
UPS	Uninterrupted power supply
USP	United States Pharmacopeia

Glossary

The definitions 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/transport/logistic services.
Controlled or Hazardous Time- and Temperature-Sensitive Drug Products	Time- and temperature-sensitive drug products (TTSDPs) with high illicit value: poisons, narcotics, psychotropic products, inflammable or explosive substances and radioactive materials.
Dunnage	Loose packing material used to protect TTSDPs from damage during transport.

External Distribution	Transport of TTSDPs 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 TTSDPs within a pharmaceutical manufacturer's internal supply chain (i.e. all internal transports from manufacturing facility to warehouse to distribution centre).
Net Storage Capacity	The total volume available for storing TTSDPs, 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	Any product intended for human use or veterinary product intended for administration to food-producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing country and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines.
Qualification	Documented testing that demonstrates, with a high degree of assurance, that a specific process will meet its predetermined acceptance criteria.
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.
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.
Service Level Agreement (SLA)/outsourced Activity	A service level agreement or contract is a negotiated agreement between the customer 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.
Storage temperature	The temperature range may include 2-8ºC for refrigerators/cold rooms, 8-15ºC for cool rooms or any other temperature range listed on the TTSDPs 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.
Substandard & Falsified (SF)	Substandard drug means a drug as defined in Section 3 (zz) of the Drugs Act, 1976. Whereas Falsified products include Spurious, Adulterated, Misbranded and Counterfeit drugs (as defined in Section 3 (zb), 3 (a), 3 (s) and 3 (f) of the Drugs Act 1976 respectively)
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 TTSDPs 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, but is not actively or passively controlled within precise redefined limits
Time and Temperature-Sensitive Drug Products	Any Pharmaceutical Product/Biologicals/Intermediates/API/ 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 TTSDPs may be exposed during transport.
Utilization Factor	The percentage of the total volume available for storing TTSDPs 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.
Validation	Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria.

The following sections provide core guidelines for the entities involved in the distribution and supply chain of TTSDs and recommends good practices to be adopted at each transitional step to maintain the quality, safety, and efficacy of these products in the entire supply chain system. These guidelines are adopted based on the Annex 9 WHO Model Guidance for the Storage and Transport of Time- and temperature–Sensitive Pharmaceutical Products (TRS No.961, 2011) and are intended to provide further interpretations of the text.

7. IMPORTATION

Long distance import of TTSDPs must be ensured in a manner that the products will be maintained within an acceptable temperature range defined as 2-8oC in majority of the cases or any other temperature range listed on the TTSDPs label, and within the regulatory documentation, for transportation/long-term storage.

Special protocols must be followed to avoid issue of temperature excursions in cold logistics.

7.1. Port handling and customs clearance

7.1.1. Port of entry

Import of TTSDPs should take place through a port of entry that is fully equipped to handle such products to minimize risk damage.

7.1.2. Offloading

Unload the Shipment of TTSDPS to safe and suitable temperature-controlled area to avoid exposure to adverse ambient conditions.

7.2. Temporary storage at port of entry

Store TTSDPs shipments in a secure warehouse maintained under the conditions recommended by the product manufacturer or product specifications, with the products clearly labelled as ‘cold chain goods for their proper storage until the shipment has been authorized for removal by customs. Ideally, TTSDPs should only arrive through those ports of entry where facilities are suitable for cold storage to avoid the increased risk of temperature excursions. If, any such excursion(s) happen that should be properly documented and investigated.

In some situations, arrangements can be made for formal customs clearance to take place away from the port of entry. In situations where the port of entry is not equipped with

suitable cold storage facilities, this can reduce the risk of temperature excursions.

7.3. Customs clearance

In Pakistan, there is a pre-clearance mechanism in practice known as ICG (Immediate Clearance Group), which is operated 24 hours and 7 days a week for the immediate clearance of perishable/temperature sensitive goods including vaccines and anti-sera. DRAP has published a guideline detailing the document and procedural requirement for import of therapeutic goods at the following link (Quality Assurance – Drug Regulatory Authority of Pakistan (dra.gov.pk) **User Manual / Guide for Online Import Export Software (OIES) English**).

7.4. Port Storage

TTSDPs should be stored in a port warehouse where it can be demonstrated that storage conditions indicated on the label are being met and recorded. Port warehouse should be equipped with calibrated monitoring devices to control and monitor temperatures in their interim storage period.

8. WAREHOUSING SITES

Manufacturers having a valid drug manufacturing license are required to establish a warehouse/ Finished Goods Store within the premises capable of storing TTSDPs in accordance with the conditions of registration / market authorization and product specifications. However, if manufacturer intends to establish a warehouse / finished goods store outside the manufacturing facility, a separate license for storage will be required under the relevant provincial drug sale rules.

Similarly, importers, distributors, stockists and other entities involved in storage and distribution of TTSDPs, will require to obtain a license for storage under the relevant provincial drug sale rules.

8.1. Site layout

Design or adapt storage areas that assure good storage conditions. Make sure they are clean and dry, with enough air circulation. Ensure they are maintained within all acceptable temperature limits and minimal human error. General storage areas should be well lit.

Develop storage sites to minimize risks from natural hazards such as floods, landslides and earthquakes and extreme weather conditions such as hurricanes and tornadoes to

protect against loss of valuable pharmaceutical products, to ensure continued supply to patients in the market and to protect personnel working in the store.

8.2. Site access

Provide vehicular access to storage buildings sufficient to accommodate the largest vehicles visiting the site, including emergency vehicles to ensure convenient operation of the facility.

8.3. Site security

Provide perimeter protection to ensure security of the grounds and storage buildings against anticipated risks like protection against vandalism, theft and other illegal incursions. Security arrangements should be appropriate to the site location and the value of goods stored there.

8.4. Site cleanliness

Keep the site free of accumulated dust, dirt, waste and debris. Ensure that pests are kept under control within the site area. Collect waste in designated closed containers and arrange for safe disposal at frequent intervals in order to protect storage buildings against ingress by dust, dirt and pests.

9. STORAGE BUILDINGS

9.1. Construction standards

Construct or procure storage buildings that are:

- purpose-designed for the storage of TTSDPs, 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;
- constructed using locally available materials and building technologies; and
- built to minimize hiding and nesting places for pests.
- 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 TTSDPs store.

Storage in unsuitable and poorly-designed buildings places TTSDPs at risk and increases storage costs. Buildings constructed using inappropriate materials and technologies are difficult to operate and maintain in resource-constrained settings.

9.2. 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 TTSDPs store.

9.3. Loading and receiving bays

9.3.1. Loading 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, snow and wind, and from extremes of heat, cold and solar radiation that could damage TTSDPs, and measures are taken to minimize pest activity in these areas to ensure protection against damage and maintenance of product quality.

9.3.2. Receiving bays

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 to protect against contamination of outgoing TTSDPs.

9.4. Goods assembly and quarantine areas

9.4.1. Goods assembly areas

Provide sufficient space to receive, assemble and pack TTSDPs for dispatch under temperature-modified conditions. Preferably, these areas should be physically close to the temperature-controlled storage area for protection of TTSDPs during arrival, order assembly and dispatch.

9.4.2. Holding area for incoming goods

Provide a temperature-controlled holding area for incoming TTSDPs 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 since incoming items may need inspection and/or regulatory clearance, including laboratory testing.

Where goods are held in bond in the warehouse, awaiting customs clearance, they must be physically separated and secured.

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

9.5. Environmental control of ancillary areas

Ensure, where possible, that ancillary areas where TTSDPs 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 high relative humidity and are not sufficiently protected by their packaging;
  Note: Active environmental control of ancillary areas may not be needed if all TTSDPs are kept in temperature-controlled packaging and/or humidity-protective packaging when passing through these areas.
- protected from undue exposure to direct sunlight;
- protected from the weather;
- protected against dust, dirt and waste accumulation;
- adequately ventilated;
- adequately lit to enable operations to be carried out accurately and safely;
- monitored during the times when TTSDPs are handled; and monitored during the times when TTSDPs are handled (see 4.5.1-4.5.4).

9.6. Building security

9.6.1. General building security

Ensure that buildings used to store TTSDPs have sufficient security to prevent unauthorized access and to prevent misappropriation of goods & to protect against vandalism, theft and other illegal incursions. Security arrangements should be appropriate to the site location and to the value of goods stored there.

9.6.2. Controlled and hazardous substances areas

Ensure that to protect property and life all areas that are used to store controlled or hazardous TTSDPs, are:

- dedicated, securely locked facilities that comply fully with all legislative and regulatory requirements applicable in the country where the store is located;
- only accessible to authorized staff;
- protected by automatic intruder and/or fire and smoke, and/or chemical and/or radiological sensor alarm systems appropriate to the type(s) of product being stored; Zoned sprinkler systems are recommended to control fires and to localize product damage in the event of system activation.
- designed to be explosion-proof, where explosive TTSDPs are stored; explosion-proof stores must have a blast roof or wall. Preferably, explosive substances should be stored in an independent building, well separated from the main store.
- continuously monitored by security staff.

9.7. Fire protection

9.7.1. Fire protection equipment

Provide suitable fire detection and fire-fighting equipment, including fire hydrants, in all TTSDPs storage areas and ensure that:

- systems and equipment are appropriate for the class of occupancy and product storage arrangements and are approved by the local fire authority; and
- equipment is regularly serviced in accordance with the equipment manufacturers' recommendations and local regulations.

9.7.2. Fire prevention, detection and control procedures

Develop & follow standard operating procedures (SOPs) for fire prevention, detection and control. Train staff and carry out regular fire drills. Prohibit smoking in all areas.

9.8. Building hygiene

9.8.1. Building cleanliness

Implement a cleaning programme for all areas to ensure protection against damage and contamination of TTSDPs and to minimize the risk of pest infestation:

- do not allow the accumulation of dust, dirt and waste, including packaging waste;
- take precautions against spillage or breakage, and cross-contamination;
- collect waste in designated closed containers and arrange for safe disposal at frequent intervals;
- do not permit consumption of food or beverages other than in designated areas; and
- maintain cleaning records to demonstrate compliance.

9.8.2. Pest control

Implement a programme to keep all areas free of pests. This should include enclosed receiving and loading bays to protect against damage and contamination of TTSDPs. Maintain records to demonstrate compliance with a robust pest control programme.

9.9. Power supply

9.9.1. Uninterrupted power supply

Where possible, and where necessary, ensure that all temperature-controlling equipment for TTSDPs storage (i.e. refrigerators, freezers, building management systems, heating, ventilation and air-conditioning (HVAC) systems, compressors, air-handling units, monitoring systems, alarms and related computer equipment) are connected to a Generator or an uninterrupted power supply (UPS) system, whichever is appropriate. An alternative approach to UPS is to use refrigeration equipment with extended holdover capacity, for example, ice-lined refrigerators, or gas, kerosene or solar-powered refrigerators. 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; The installed capacity of the UPS system can be minimized by fitting electronic controls which reduce compressor start-up loads.
- not exceed the defined parameters of the mains power supply;
- be equipped with automatic mains 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.

9.9.2. Power failure contingency plan

Develop and maintain a contingency plan to protect TTSDPs in the event of power failure which places products at risk. Alternative emergency cooling systems (e.g. liquid nitrogen or dry ice) are acceptable.

9.10. Building maintenance

Implement a planned preventive maintenance programme to ensure that storage buildings and building utilities are well maintained so that storage buildings continue to protect stored products against damage. Keep records to demonstrate compliance with the programme.

10. TEMPERATURE-CONTROLLED STORAGE

10.1. Normative references

- EN 60068-3 parts 5, 6, 7 and 11: *Environmental testing. Guidance. Confirmation of* the performance of temperature chambers
- International Air Transport Association (IATA) *Perishable cargo regulation.* current edition,
- USP <1079>*Good storage and shipping practices*
- USP <1118>*Monitoring devices — time, temperature and humidity*

10.2. Storage capacity of temperature-controlled stores

Ensure that the net storage capacity of the temperature-controlled stores is sufficient to accommodate peak TTSDPs 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. It will help 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 (EEFO)). Overstocking makes FIFO or EEFO handling difficult or impossible and hinders accurate physical stock counts.

10.3. Temperature-controlled storage

Ensure that TTSDPs 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;
- preferably 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 TTSDPs that are damaged by exposure to low temperatures;
- connected to a UPS as described in clause 3.9.1;
- equipped with a calibrated continuous temperature monitoring system with sensors located at points representing greatest temperature variability and temperature extremes;
- preferably 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 4.7.

To maintain labelled TTSDPs storage temperatures during long-term storage, Refrigerators and freezers should be:

- purpose-designed for the storage of TTSDPs; household-style units are only acceptable if they have been independently tested and found to comply with the temperature control requirements of a recognized standard for pharmaceutical refrigerators and freezers;(For example, WHO PQS standards for refrigerators and freezers are available at: http://www.who.int/immunization_standards_/vaccine quality/pqs_e03_fridges_freezers/en/index.html.
- capable of maintaining the temperature range specified by the TTSDPs 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 and/ or refrigeration failure;
- fitted with lockable doors or lids, or access control system, as necessary; and
- qualified and/or tested as defined in clause 4.7.

Refrigerators without freezers and stand-alone freezers usually perform better at maintaining the precise temperatures required for vaccine storage. Vaccines should be stored centrally in the refrigerator or freezer, not in the door or on the bottom of the storage unit, and sufficiently away from walls to allow air to circulate.

10.4. Temperature-controlled storage for controlled and hazardous products

To protect this category of TTSDPs against theft and misuse and to safeguard workers and general storage areas in the event of an accident involving hazardous substances, ensure that controlled and hazardous TTSDPs are securely stored:

- Provide dedicated temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers for these TTSDPs, in separate secure areas, as described in clause 3.6.2. & in accordance with DRAP Act, 2012, Control of Narcotic Substances Act, 1997 & Control of Narcotic Substances (Regulation of Drugs of Abuse, Controlled Chemicals, Equipment & Materials) Rules, 2001
- Alternatively, bulk stocks of TTSDPs with high illicit-value may be stored in a securely locked section of a general temperature-controlled storage area.

10.5. Temperature and humidity control and monitoring in storage

10.5.1. Temperature control

Preferably provide thermostatic temperature control systems for all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSDPs in order to maintain labelled TTSDPs temperatures during long-term storage. Thermometers provide only limited and discontinuous temperature information. For this reason, continuous recording devices are preferable. 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 4.10.1;
- 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,
- control sensors independent of the temperature monitoring system.

10.5.2. Temperature monitoring

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

General requirements

- Monitoring sensors accurate to ± 0.5 °C or better for electronic devices and ± 1 °C or better for alcohol, bi-metal gas or vapour pressure thermometers.
- Monitoring sensors calibrated as described in clause 4.10.1.
- 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 4.7.
- 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 in the event of a power failure. Where there is no UPS, the autonomy period for the device should be matched to the maximum length of anticipated power outages.

Refrigerators and freezers

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

10.5.3. Humidity control

Provide humidity control in temperature-controlled rooms that are used to store TTSDPs which are adversely affected by high relative humidity and are not sufficiently protected by their packaging. Such products are typically labelled “store in a dry place”, or carry similar wording and require a humidity-controlled environment.

10.5.4. Humidity monitoring

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

- sensors accurate to ± 5% RH;
- sensors calibrated as per clause 4.10.2;
- sensors located to monitor worst-case humidity levels within the qualified storage volume defined in clause 4.7;
- 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. Where there is no UPS the autonomy period for the device should be matched to the maximum length of anticipated power outages.

10.6. Alarm systems

10.6.1. Temperature alarms

Provide temperature alarm systems for temperature-controlled rooms, cold rooms, freezer

rooms, refrigerators and freezers, used to store TTSDPs. Comply with the following minimum requirements:

General requirements

- Sensors accurate to ± 0.5 °C.
- Sensors calibrated as described in clause 4.10.1.
- Sensors located to monitor worst-case temperatures within the validated storage volume defined in clause 4.7; 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.

Temperature-controlled rooms, cold rooms and freezer rooms

- High/low alarms set points to trigger appropriately located visual alarm(s).
- Preferably there should also be appropriately located audible alarm(s) in addition to the visual 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.

Refrigerators and freezers

- Preferably there should be a visual and/or audible alarm system; this may be integrated with a portable continuous temperature monitoring device.

10.6.2. Humidity alarms

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

- sensors accurate to ± 5% relative humidity (RH);
- sensors calibrated as described in clause 4.10.2;
- sensors located to monitor worst-case humidity levels within the validated storage volume defined in clause 4.7; 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;
- high/low alarms set points to trigger appropriately located visual alarm(s);
- preferably there should also be appropriately located audible alarm(s) in addition to the visual alarm(s); and
- 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.

10.7. 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 TTSDPs (for example areas in close proximity to cooling coils, cold air streams or heat sources); and
- 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 TTSDPs. Independent testing must be carried out between the chosen set points and under the ambient temperature conditions to which the equipment will be exposed during operation. Prequalified equipment of this type must be correctly installed in each location in accordance with written guidance.

10.8. Cleanliness of temperature-controlled stores

Implement a cleaning and decontamination programme for all temperature-controlled rooms to protect against damage and contamination of TTSDPs and hazards to workers, arising from spillage or breakage.

- 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.

10.9. 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 TTSDPs 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.

10.10. Calibration and verification of control and monitoring devices

10.10.1. Calibration of temperature control and monitoring devices

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.

10.10.2. Calibration of humidity control and monitoring devices

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.

10.10.3. Alarm equipment verification

Check functionality of temperature and humidity alarms at least once every six months at the designated set points to ensure that labelled TTSDPs storage temperatures and humidity control can be maintained during long-term storage.

Maintain records to demonstrate compliance.

11. MATERIALS HANDLING

11.1. 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 for protection of the workforce.

12. TRANSPORT AND DELIVERY

12.1. Normative references

- EN 13428:2004. *Packaging. Requirements specific to manufacturing and composition. Prevention by source reduction.*
- EN 13430:2004. *Packaging. Requirements for packaging recoverable by material recycling.*
- EN 13431:2004. *Packaging. Requirements for packaging recoverable in the form of energy recovery, including specification of minimum inferior calorific value.*
- EN 13432:2000. *Packaging. Requirements for packaging recoverable through composting and biodegradation. Test scheme and evaluation criteria for the final acceptance of packaging.*
- IATA *Perishable Cargo Regulations*.
- *Isothermal and refrigerating containers for health products — Thermal performance qualification method.*
- ISTA — 5B: *Focused Simulation Guide for Thermal Performance Testing of Temperature Controlled Transport Packaging.*
- ISTA — 7D: *Thermal Controlled Transport Packaging for Parcel Delivery System Shipment. Basic Requirements: atmospheric conditioning, vibration and shock testing.*
- WHO Technical Report Series, No. 937, 2006. Annex 5: *Good distribution practices for pharmaceutical products.*

12.2. Product stability profiles

In order to protect against degradation, transport TTSDPs in such a manner that transport temperatures meet local regulatory requirements at the sending and receiving sites and/or so that temperature excursions above or below the manufacturer's labelled storage temperature range do not adversely affect product quality. Product stability data must demonstrate the acceptable temperature excursion time during transport.

12.3. Transport route profiling and qualification

Profile and qualify transport routes to ensure that TTSDPs can be safely transported within the transport temperature profile defined for each product:

- Select the most suitable methods for protecting TTSDPs 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.

12.4. Temperature-controlled transport

12.4.1. Air and sea transport

Ensure that any carrier contracted to transport TTSDPs by air or by sea 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.

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 so as to ensure that the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product.

12.4.2. Temperature-controlled road vehicles generally

Ensure that temperature-controlled road vehicles used for the transport of TTSDPs are:

- 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 TTSDPs that are damaged by exposure to low temperatures;
- equipped with calibrated temperature monitoring devices with sensors located at points representing temperature extremes;
- 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;
- qualified as defined in clause 6.6; and
- regularly calibrated and maintained and records kept to demonstrate compliance.

12.4.3. Transport of controlled TTSDPs and TTSDPs with high illicit value

For prevention of theft & misappropriation of this category of TTSDPs as well as to safeguard the driver, ensure that controlled TTSDPs and TTSDPs with high illicit value are transported in the following manner:

- Transport practices comply with all relevant applicable legislation and regulations.
- Vehicles are equipped with lockable doors and an intruder alarm.
- Vehicles use unique seal lock indicating devices such as cable seal locks with unique identifiers that are tamper-resistant to protect against unauthorized access during transit. (Refer to ISO/PAS 17712: *Freight containers — Mechanical seals)*
- Security-cleared delivery drivers are employed.
- All deliveries are documented and tracked.
- Signed dispatch and arrival records are kept.
- Shipments are fitted with security equipment appropriate to the product being transported and the assessed security risk, such as global positioning system (GPS) devices located in the vehicle and/or hidden in the product.
- Drivers are informed about the perishability of the product and the maximum acceptable transport time.

12.5. Temperature and humidity control and monitoring during transit

12.5.1. Temperature control in temperature-controlled road vehicles

Provide thermostatic temperature control systems for all temperature-controlled vehicles used to transport TTSDPs. Comply with the following minimum requirements:

- system able continuously to maintain air temperatures within the set point limits throughout the validated storage volume defined in clause 6.6;
- control sensors accurate to ± 0.5 °C;
- control sensors calibrated as described in clause 6.7.1;
- control sensors located to control worst-case temperatures in order to maximize available safe storage volume;
- control sensors positioned in the return air stream; and
- control sensors independent of the temperature monitoring system.

12.5.2. Temperature monitoring in temperature-controlled road vehicles

Provide air temperature monitoring systems and devices for vehicles used to transport TTSDPs. Comply with the following minimum requirements:

- monitoring sensors accurate to ± 0.5 °C;
- monitoring sensors calibrated as described in clause 6.7.2;
- monitoring sensors located to monitor worst-case temperatures within the qualified storage zone defined in clause 6.6;
- monitoring sensors positioned so as to monitor worst-case positions;
- provide a temperature record with a minimum recording frequency of six times per hour for each sensor position; (Recording frequency should take account of the storage capacity of the data logger and the expected transport period) and
- provide documentation which can be stored and accessed.

Establish transit temperature specifications and document transit temperatures for every internal and external shipment.

12.5.3. Humidity monitoring in temperature-controlled road vehicles

Preferably provide humidity monitoring systems and devices for temperature-controlled vehicles which are used to transport TTSDPs that require a humidity-controlled environment. Systems and devices should comply with the following minimum requirements:

- sensors accurate to ± 5% RH;
- sensors calibrated as described in clause 6.7.3;
- sensors located to monitor worst-case humidity levels within the qualified storage zone defined in clause 6.6;
- sensors positioned so as to be minimally affected by transient events such as door opening;

- provide a humidity record with a minimum recording frequency of six times per hour for each sensor position; and
- provide documentation which can be stored and accessed.

Establish transit humidity specifications and document transit humidity conditions for internal and external shipments where required.

12.5.4. Temperature monitoring in passive and active shipping containers

To ensure that TTSDPs can be safely transported within the transport temperature profile defined for each product, use chemical or electronic freeze indicators, electronic loggers (with or without alarms) and/or other suitable indicators to monitor temperature and/or humidity exposure during internal distribution. Preferably use these devices for external distribution. Monitor and document indicator status upon arrival.

12.6. Qualification of temperature-controlled road vehicles

Where temperature-controlled vehicles are directly owned and/or operated, qualify each vehicle before it becomes operational, wherever possible to ensure that TTSDPs can be safely transported within the transport temperature profile defined for each product. 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 TTSDPs (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; and
- 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 each example when a new vehicle becomes operational.

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

12.7. Calibration and verification of transport monitoring devices

12.7.1. Calibration of transport temperature control devices

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

12.7.2. Calibration of transport temperature monitoring devices

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

12.7.3. Calibration of transport humidity monitoring devices

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

12.7.4. 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, unless otherwise justified.

Maintain records to demonstrate compliance.

12.8. Shipping containers

12.8.1. Container selection generally

For Quality assurance and safety, 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.

12.8.2. 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 TTSDPS within the product's stability profile as stated by the product manufacturer and/or to maintain the TTSDPS within the transit temperature specification requirements specified by the regulatory authorities at both the sending and receiving locations.

12.8.3. 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 TTSDPS within the temperature range needed to meet the product stability profile 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.

12.8.4. Qualification of active containers

Qualify active containers:

- ensure that the container is capable of maintaining the TTSDPs within the temperature range needed to meet the product stability profile 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.

12.9. Shipping container packing

Ensure that shipping containers are systematically used in the manner defined during the container qualification process by packing TTSDPs shipping containers to:

- the exact specified configuration to ensure that the correct TTSDPs 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 contamination or attack by microorganisms and pests;
- 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; and
- ensure that packages containing dangerous goods (including dry ice) are labelled in compliance with relevant transport regulations and requirements.

12.10. Product handling during packing and transport

To maintain TTSDPS quality during transport, handle TTSDPs correctly during packing

and transport:

- pack TTSDPs in an area set aside for the assembly and packaging of these products as specified in clause 3.3.1;
- take precautions against spillage or breakage, contamination and cross-contamination;
- deliver TTSDPs to outside recipients by the most suitable mode(s) of transport available in order to minimize delivery time; and
- ensure that patients receiving TTSDPs deliveries are given clear advice on correct storage of the product before use.

12.11. Cleaning road vehicles and transport containers

Implement a cleaning and decontamination programme for all road vehicles and reusable shipping containers used to transport TTSDPs for protection against damage and contamination of TTSDPs and hazards to workers arising from spillage or breakage.

- 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.

12.12. Transport of returned and recalled TTSDPs

12.12.1. Transport of returned TTSDPs

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

- the sender and recipient must work together so that that the product is maintained within the temperature range needed to meet the manufacturer's stated product stability profile;
- 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 TTSDPs 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.

This will ensure that returned and recalled TTSDPs are maintained within the correct transport temperature profile so that they can safely be re-stocked if a decision to do so is made.

12.12.2. Transport of recalled TTSDPs

Ensure that recalled TTSDPs 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 as described in clause 8.6.3.

12.13. Packaging & Transport of Vaccines

For transport, Packaging & Shipping of vaccines WHO's "Guidelines on the International Packaging & Shipping of Vaccines" WHO/IVB/05.23, shall be followed.

12.14. Transport of TTSDPs containing Controlled Substances

In addition to the general provisions as mentioned above, transport of TTSDPs containing Controlled Substances will be carried out in accordance with DRAP Act, 2012, Control of Narcotic Substances Act, 1997 & Control of Narcotic Substances (Regulation of Drugs of Abuse, Controlled Chemicals, Equipment & Materials) Rules, 2001) as well as applicable Provincial Drug Sales Rules also.

13. LABELLING

13.1. Normative references

- *IATA Perishable Cargo Regulations*

13.2. Labelling

13.2.1. Labelling generally

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

- identify the product in accordance with The Drugs (Labelling & Packing) Rules, 1986 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.

13.2.2. Labelling air-freighted shipments

In cases where TTSDPs are to be air-freighted, the package(s) should be labelled using the standard International Air Transport Association (IATA) time and temperature-sensitive symbol, in accordance with the conditions outlined in IATA Perishable Cargo Regulations to ensure that products are correctly and safely handled at all points in the supply chain. Apply the label to the outer surface of individual shipping packages, over-

packs or bulk containers.

14. STOCK MANAGEMENT

14.1. Stock control systems

14.1.1. General stock control systems and procedures

TTSDPs stock control systems and procedures meet the following minimum requirements to ensure that accurate and complete stock records are kept at all times:

- allow access only to authorized persons;
- record all receipts and dispatches;
- record batch numbers and expiry dates;
- record short-dated and expired products;
- record product status (i.e. released, quarantined, hold, reject);
- record all product returns, recalls, withdrawals, damage and disposals;
- manage the issue of products in EEFO order; and
- take regular physical inventories and reconcile stock records with the actual physical count.

Investigate and report on stock discrepancies in accordance with agreed procedures. Preferably physical counts should be made at least twice a year.

14.1.2. Stock control procedures for controlled and hazardous TTSDPs

In addition to the requirements set out in clause 8.1.1, implement the following procedures to ensure that accurate and complete stock records are kept at all times and to satisfy the requirements of the regulatory authorities:

- Institute a customer verification process to ensure that all recipients of these products are authorized to receive them.
- Maintain stock records which specifically identify products in these categories.
- Carry out regular audits and make audit reports available to the responsible authorities.
- Comply with all record-keeping procedures specified in DRAP Act, 2012, Control of Narcotic Substances Act, 1997 & Control of Narcotic Substances (Regulation of Drugs of Abuse, Controlled Chemicals, Equipment & Materials) Rules, 2001. Retain product transaction and delivery records for at least the minimum time period required by local regulations.

14.2. Incoming goods

14.2.1. Product arrival checks

Check and record the following for all incoming TTSDPs:

- 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; 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; and
- verify that required storage and transport conditions have been maintained.

14.2.2. Actions following arrival checks

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

- 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/falsified. Do not release until checks have been completed satisfactorily.
  All unacceptable temperature excursions should be evaluated to determine their effect on the product.
- Report any defects to the supplying store or holder of the marketing authorization.
- Do not transfer to saleable stock until all relevant disposition procedures have been completed.

14.3. Outgoing goods (external deliveries)

14.3.1. 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 EEFO 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 EEFO 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.

14.3.2. Actions following dispatch

In order to ensure that outgoing TTSDPs 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, monitor TTSDPs following dispatch by:

- tracing products to their intended destination;
- recording and retaining records to provide assurance of goods arrival status. A suitable delivery report from the carrier is an acceptable alternative; and
- taking appropriate action in the event of returns, recalls or complaints.

14.4. Product complaint procedures

To ensure protection of the public and of the reputation of the supplying organization, manage product complaints as follows:

- If a product defect is discovered or suspected in a batch of TTSDPs, cooperate with the regulatory authorities to determine whether other batches are affected and recall products if required to do so by the regulatory authority.
- Where complaints or defects relate to a product or its packaging, immediately notify the holder of the marketing authorization for the product.
- Where complaints or defects arise as a result of errors or omissions within the organization, immediately evaluate the causes and take remedial measures to prevent a recurrence.
- Record all complaints and the remedial actions taken. Monitor and analyse trends in the complaint records.

14.5. Substandard & Falsified product procedures

14.5.1. Substandard & Falsified products

For protection of the public, protection of legitimate suppliers and manufacturers and conformity with regulatory requirements, implement systems for identifying and managing substandard & falsified products found in the supply chain as follows:

- Physically segregate any substandard & falsified TTSDPs found in the supply chain and store securely until legal investigations are complete.
- Label them clearly as “Not for use” or other similar phrase;
- Immediately notify the regulatory authorities (DRAP and/or Provincial drug Control Units), as well as the holder of the marketing authorization of the product.
- Cooperate with regulatory authorities to assist with investigating the source of substandard & falsified products and implement appropriate remedial action(s).

- Document the decision-making process for disposal or return of condemned or defective TTSDPs and make these records available to the relevant authorities.

14.6. Product return, recall, withdrawal and disposal procedures

14.6.1. Return procedures

Manage product returns as follows:

- Quarantine returned TTSDPs 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 TTSDPS.
- If returned stock is re-issued, distribute in EEFO order or in accordance with the exposure status of any product-mounted time-temperature indicator device.
- Quarantine returned TTSDPs that have been exposed to unacceptable storage and/or transport temperatures and mark for disposal.
- Maintain records of all returned TTSDPs.

14.6.2. Recall procedures

Manage product recalls as follows:

- Conduct local urgent and non-urgent TTSDPs recalls in accordance with "GUIDELINES ON RECALLS AND RAPID ALERTS OF DEFECTIVE THERAPEUTIC GOOD" published on DRAP's website.
- Notify overseas regulatory counterparts where the product has been exported.
- Notify all affected customers as applicable.
- Quarantine any remaining inventory of recalled TTSDPs and mark for further investigation before disposal.
- Maintain records of all TTSDPs recalls, including reconciliation of quantity sold, quantity returned, quantity remaining or quantity consumed.

14.6.3. Disposal procedures

Manage product awaiting board of survey or disposal as follows:

- Ensure that rejected and/or recalled or withdrawn TTSDPs cannot be used, released or cause contamination to other products. Store separately from other products, in accordance with local regulations, to await destruction or return to the supplier.
- Safely dispose of rejected and/or recalled/withdrawn products in accordance with local regulations (DRAP Act, 2012, Control of Narcotic Substances Act, 1997 & Control of Narcotic Substances (Regulation of Drugs of Abuse, Controlled Chemicals, Equipment & Materials) Rules, 2001), including where relevant, regulations covering the disposal of hazardous and controlled drugs.
- Maintain disposal records.

14.7. Traceability or stock tracking

Ensure that stock and distribution records enable traceability, or stock tracking, of TTSDPs from the point of supply to the end-user or patient to demonstrate that TTSDPs have been correctly distributed.

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 (if any), status of product-based time-temperature indicators (if any) and physical condition of goods and time of receipt;
- for outgoing goods: type of shipping indicators used (if any), status of product-based time-temperature indicators (if any) and physical condition of goods and time of dispatch.

Monitor, record, and investigate discrepancies.

15. GENERAL PROCEDURES AND RECORD-KEEPING

15.1. Emergencies and contingency planning

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

- extended power supply outages;
- equipment failure; and
- vehicle breakdown during transport of TTSDPs.

Prepare action plans to deal with products subjected to temperature excursions.

Ensure that the responsible staff know, and have rehearsed, the appropriate actions to be taken in the event of the identified emergency scenarios.

15.2. General record-keeping

15.2.1. 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;
- labelled, 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; and
- 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.

15.2.2. Content of records

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

- status of product on arrival;
- temperature and humidity records including records of excursions outside labelled storage and/or transit temperature specification conditions;
- general TTSDPs stock transactions, including purchase and sale records;
- controlled drug audits;
- audits for products with high illicit value;
- audits for hazardous products;
- stock tracking;
- return, recall, withdrawal and disposal reports, where relevant;
- product complaint reports, where relevant; and
- counterfeit product reports, where relevant.

Maintain all records in accordance with local legislation and regulations.

15.2.3. Record review and retention

Ensure that records are reviewed and approved on a regular basis by a designated member of the quality management team. Ensure that records are accessible for review by end-users, the regulatory authority and other interested parties. Retain records for the minimum period required under local legislation, but for not less than three years.

15.3. Temperature and humidity records

15.3.1. 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 the shelf-life of the stored material or product, or as long as required by national legislation.

15.3.2. Humidity records

When storing products which are adversely affected by high relative humidity (see clause 4.5.3), 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 in accordance with Drugs (Licensing, registering & Advertising) Rules, 1976.

16. ENVIRONMENTAL MANAGEMENT

16.1. Normative references

- ISO 14001: 2004. *Environmental management systems — Requirements with guidance for use.*
- *The Montreal Protocol on Substances that Deplete the Ozone Layer.* UNEP, 2000.

16.2. Environmental management of refrigeration equipment

To comply with international protocols and accords on climate change and environmental protection, ensure that all new refrigeration equipment for temperature-controlled storage and transport is specified to:

- use refrigerants that comply with the Montreal Protocol;
- minimize or eliminate the use of refrigerants with high global warming potential (GWP); and
- minimize CO_2 emissions during operation.

Select equipment to minimize whole-life environmental impact and employ best practice to eliminate leakage of refrigerant into the environment during installation, maintenance and decommissioning of refrigeration equipment.

17. QUALITY MANAGEMENT

17.1. Normative references

- ICH, 2005: *ICH Harmonized Tripartite Guideline: Quality risk management Q9*
- ISO 9000:2005. *Quality management systems — Fundamentals and vocabulary*
- ISO 9001:2008. *Quality management systems — Requirements*

- ISO 9004:2000. *Quality management systems — Guidelines for performance improvements*
- ISO 10005:2005. *Quality management systems — Guidelines for quality plans*
- ISO 19011:2002. *Guidelines for quality and/or environmental management systems auditing*

17.2. Organizational structure

Establish, document and maintain an organizational structure for the TTSDPS storage and shipping and distribution operations which clearly identifies all key management responsibilities, and the personnel who are accountable.

17.3. Quality systems

17.3.1. Quality system

Establish, document and maintain a quality system for the management of TTSDPs including, the following, as applicable:

- standard quality system(s) and associated auditing procedures;
- written procedures and specifications;
- record storage, record retention and record destruction programme;
- risk management;
- calibration programme;
- stability programme;
- qualification and validation programme;
- deviation and root cause investigation programme;
- corrective and preventive action (CAPA) procedures;
- training programme;
- periodic temperature-controlled process assessment;
- change control programme;
- maintenance programme;
- management controls;
- product return and recall/withdrawal policies, including emergency recalls;
- product complaint policies;
- material destruction programme;
- warehouse and storage programme;
- shipping and distribution programme;
- notification systems for regulatory agencies; boards of health and ministries of health; and
- self-inspection programme and continuous quality improvement.

Carry out annual reviews of the quality management system to ensure that it remains appropriate, relevant, and effective.

17.3.2. Self inspections

Conduct regular self-inspections to ensure continuing compliance with quality

management standards GSP and GDP; record results, follow-up with the corrective actions needed to rectify areas of non-compliance and document the changes made.

17.3.3. Contractors subject to service level agreements

To demonstrate compliance with applicable quality management standards, ensure that every contractor with whom there is an SLA provides periodic evidence of compliance with the GSP and/or GDP standards incorporated into the SLA.

17.4. Management of documents and standard operating procedures

17.4.1. Standard operating procedures

Develop and maintain SOPs covering correct storage, internal shipping and external distribution of TTSDPs, including, but not limited to, the following topics:

- security, including management of controlled and hazardous TTSDPs;
- safe handling of TTSDPs;
- temperature monitoring;
- calibration of temperature and humidity monitoring devices and alarm systems;
- qualification and validation procedures, including temperature mapping;
- maintenance of controlled-temperature equipment;
- facility cleaning and pest control;
- facility maintenance;
- product arrival (receiving) procedures and records;
- stock storage and warehousing procedures (put away, replenishment, order fulfillment, packing);
- stock control procedures and records;
- distribution procedures and records;
- management of temperature excursions;
- product return and recall/withdrawal procedures and records;
- product complaint procedures and records;
- safe disposal of damaged, expired and quarantined products and records which are no longer required;
- temperature-controlled packaging and route qualification;
- temperature-controlled vehicle operation, including management of security locks and seals;
- emergency response procedures; and
- environmental management.

Ensure that all documents are clear and unambiguous and that document change control procedures are in place as specified in clause 11.5.

17.5. Document control

Ensure that all quality manuals, SOPs and similar documents are:

- authorized by an appropriate person;

- recorded in a document register;
- regularly reviewed and kept up to date, with all changes recorded and authorized;
- version controlled;
- issued to all relevant personnel; and
- withdrawn when superseded.

Withdraw superseded documents and retain record copies for document history files and for the minimum period(s) required by the regulatory authorities and for duty-of-care purposes.

18. PERSONNEL/ TRAINING

18.1. Training

18.1.1. General training

Provide regular and systematic training for all relevant personnel responsible for storage, loading and unloading areas used for non-hazardous TTSDPs to ensure that all relevant personnel are competent to carry out their duties, covering the following:

- applicable pharmaceutical legislation and regulations;
- SOPs and safety issues; and
- Response to emergencies.

Ensure that each employee understands his or her specific responsibilities. Provide similar training for drivers who are responsible for transporting these substances. Maintain individual training records to demonstrate compliance and regularly evaluate the effectiveness of training programmes.

18.1.2. Specialist training

In addition to the training described in clause 12.1.1, provide regular and systematic additional training for relevant personnel responsible for storage, loading and unloading of controlled or hazardous TTSDPs to ensure that all relevant personnel are competent to handle controlled or hazardous TTSDPs.. Training should cover the following:

- applicable legislation and regulations;
- security and safety risks; and
- response to emergencies.

Ensure that each employee understands his or her specific responsibilities. Maintain training records to demonstrate compliance and perform effectiveness checks on training. Provide similar training for drivers who are responsible for transporting these substances.

19. REFERENCES

i. The Drugs Act, 1976

ii. The Drug Regulatory Authority of Pakistan Act, 2012

iii. Control of Narcotic Substances Act, 1997 &

iv. Control of Narcotic Substances (Regulation of Drugs of Abuse, Controlled Chemicals, Equipment & Materials) Rules, 2001

v. Annex 9 WHO model guidance for the storage and transport of time- and temperature–sensitive pharmaceutical products (TRS No.961, 2011)

vi. ISO/PAS 17712: *Freight containers — Mechanical seals*

vii. www.who.int/immunization_standards/vaccinequality/pqs_e03_fridges_freezers/en/index.html

viii. "Guidelines on the International Packaging & Shipping of Vaccines" WHO/IVB/05.23

ix. IATA Perishable Cargo Regulations, International Air Transport Association.

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