Model requirements for the storage and transport of time and temperature sensitive pharmaceutical products

Version 2b

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Contents

Acronyms

CAPA	Corrective and Preventive Action (procedures)
EEFO	Earliest-Expiry-First-Out
GPS	Global Positioning System
IATA	International Air Transport Authority
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
TTSPP	Time and Temperature-Sensitive Pharmaceutical Product
UPS	Uninterrupted Power Supply

Glossary

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.

Controlled or hazardous TTSPPs: Temperature-sensitive pharmaceutical products 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, buying groups, etc), to clinical facilities or direct to the patient).

Internal distribution: Transport of a TTSPP 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 TTSPPs, taking account of the type of load support system employed (floor standing pallets, adjustable pallet racking, shelving units, etc.), 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.

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 state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. It does not, however, include medical devices[1].

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

Qualification: Documented testing that demonstrates with a high degree of assurance that a specific process will meet its pre-determined acceptance criteria[2].

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 (commonly referred to as a Quality Agreement), 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[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. Standard operating policies and procedures can be effective catalysts to drive performance improvement and improve organizational results.

Storage temperature: The temperature range listed on the TTSPP label, and within the regulatory filings, 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.

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 pre-defined limits.

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 pre-defined limits.

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

Time and temperature sensitive pharmaceutical product (TTSPP)*:* Any pharmaceutical good or product which, when not stored or transported within pre-defined environmental conditions and/or within pre-defined 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 TTSPP may be exposed during transport.

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[1] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. *Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments*.

[2] Definition from PDA Technical Report No. 39, 2007.

[3] Definition from IATA, Chapter 17, 9th Edition, June 2009.

Utilization factor: The percentage of the total volume available for storing TTSPPs that can reliably be achieved in practice, taking account of the types of 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 pre-determined acceptance criteria[4].

Introduction

This guideline sets out the principal requirements for the safe storage and distribution of time and temperature-sensitive pharmaceutical products (TTSPPs). It is based upon existing regulations and best practice guidance from a wide range of international sources (see Annex 1), whilst accepting that local legislation and regulations will continue to take precedence. The target audience includes regulators, logisticians and pharmaceutical professionals in industry, government and the international agencies.

The document has been prepared in close consultation with the *WHO Task Force on Regulatory Oversight on Pharmaceutical Cold Chain Management* which has been central to the review process. A full list of members is given in Annex 3.

The intention is that the listed requirements should be directly applicable in less developed countries as well as in the industrialized world. To this end, supplementary materials will be developed to show how the requirements can practicably be achieved, particularly in resource-constrained settings.

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 general guides to Good Manufacturing Practice (GMP), 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.

Key to conventions used

The following conventions are used in the requirements clauses:

- The imperative voice is used to denote a mandatory or highly desirable requirement. For example: '**Ensure that** ……..', '**Provide**……, etc.
- The phrase '**where possible'** is used to denote an optional but desirable requirement.
- Many clauses are followed by a brief explanation setting out the underlying **reason** for including the clause.

[4] Definition from PDA Technical Report No. 39, 2007.

1. Importation

1.1 Port handling and customs clearance

1.1.1 Port of entry

Where possible, import TTSPPs through a port of entry that is equipped to handle such products.

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.

Reason: To minimize the risk of theft and to 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 authorised for removal by customs[5].

Reason: To avoid risk of theft or 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. Where possible, customs staff should be supported and assisted during the clearance process by personnel with suitable pharmaceutical training, especially when clearance involves the opening and re-sealing of temperature-controlled packaging.

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

2. Warehousing sites

2.1 Site layout

2.1.1 Natural hazards

Select and/or develop storage sites to minimize risks associated with flooding, hurricanes, tornados, landslides, earthquakes and other extreme weather conditions and natural hazards.

[5] In some situations, arrangements can be made for formal customs clearance to take place away from the port of entry – for example, at a national vaccine store. In situations where the port of entry is not equipped with suitable cold storage facilities, this can reduce the risk of temperature excursions.

Reason: 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.

2.1.2 Site access

Provide vehicular access to storage buildings sufficient to accommodate the largest vehicles visiting the site, including emergency vehicles.

Reason: To ensure convenient operation of the facility.

2.2 Site security

Provide perimeter protection to ensure security of the grounds and storage buildings against anticipated risks.

Reason: To protect against vandalism, theft and other illegal incursions. Security arrangements should be appropriate to the site location and the value of goods stored there.

2.3 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.

Reason: To help protect storage buildings against ingress by dust, dirt and pests such as rodents, bats, birds and insects.

3. Storage buildings

3.1 Construction standards

Construct or procure storage buildings that are:

- purpose-designed for the storage of TTSPPs, or adapted for this purpose;
- suited to the climate, and designed to minimize energy consumption;
- built to minimize hiding and nesting places for pests;
- constructed using materials and finishes that are robust and easy to clean.

Reason: Storage in unsuitable buildings places TTSPPs at risk.

3.2 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 TTSPP store.

3.3 Goods assembly and quarantine areas

3.3.1 Goods assembly areas

Provide sufficient space to receive, assemble and pack TTSPPs for dispatch under temperature-modified conditions. Preferably these areas should be physically close to the temperature-controlled storage area.

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

3.3.2 Quarantine area

Provide a quarantine area for the isolation of returned, faulty, recalled and otherwise withdrawn goods pending 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.

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

3.4 Loading bays

3.4.1 Loading bays

Ensure that receiving and dispatch bays are protected from dust, dirt, rain and snow and wind, and from extremes of heat, cold and solar radiation that could damage TTSPPs.

Reason: Protection against damage and maintenance of product quality.

3.4.2 Receiving bays

Provide receiving areas with suitable equipment to clean containers of incoming materials and pharmaceutical products before the containers are stored.

Reason: Protection against contamination of TTSPPs.

3.5 Environmental control of ancillary areas

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

- maintained at temperature and humidity levels appropriate to the goods being handled[6];
- monitored during the times when TTSPPs are handled;
- protected from undue exposure to direct sunlight;
- protected from the weather;

[6] Active environmental control of ancillary areas may not be needed if all TTSPPs are kept in temperature-controlled packaging and/or humidity-protective packaging when passing through these areas.

- protected against dust, dirt, and waste accumulation;
- adequately ventilated;
- adequately lit to enable operations to be carried out accurately and safely.

Reason: Protection of TTSP quality during arrival, order assembly or dispatch.

3.6 Building security

3.6.1 General building security

Ensure that buildings used to store TTSPPs have sufficient security to prevent unauthorized access and to prevent misappropriation of goods.

Reason: To protect against vandalism, theft and other illegal incursions. Security arrangements should be appropriate to the site location and the value of goods stored there.

3.6.2 Controlled and hazardous substances areas

Ensure that all areas that are used to store controlled or hazardous TTSPPs 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[7];
- designed to be explosion-proof, where explosive TTSPPs are stored;
- continuously monitored by security staff.

Reason: Protection of property and life.

3.7 Fire protection

3.7.1 Fire protection equipment

Provide suitable fire detection and fire-fighting equipment in all TTSPP storage areas and ensure that equipment is regularly serviced in accordance with the equipment manufacturers' recommendations and local regulations.

Reason: Protection of property and life.

3.7.2 Fire-fighting prevention, detection and control procedures

Follow standard operating procedures for fire prevention, detection and control. Train staff and carry out regular fire drills. Prohibit smoking in all areas.

Reason: Protection of property and life.

[7] Zoned sprinkler systems are recommended to control fires and to localize product damage in the event of system activation.

3.8 Building cleanliness

3.8.1 Building cleanliness

Implement a cleaning programme for all receiving areas, storage areas, goods assembly areas and loading bays:

- 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 in receiving areas, storage areas, goods assembly areas or loading and dispatch bays.
- Maintain cleaning records to demonstrate compliance.

Reason: Protection against damage and contamination of TTSPPs and to minimize the risk of pest infestation.

3.8.2 Pest control

Implement a programme to keep storage buildings, receiving bays, goods assembly and loading bays free of pests, including enclosed receiving and loading bays. Maintain records to demonstrate compliance with a robust pest control programme.

Reason: Protection against damage and contamination of TTSPPs.

3.9 Uninterrupted power supply

3.9.1 Uninterrupted power supply

Where possible, and where necessary[8], ensure that all temperature controlling equipment for TTSP storage (i.e. refrigerators, freezers, building management systems, HVACs, compressors, air handling units, monitoring systems, alarms and related computer equipment are connected to a UPS system. Generators, where used should:

- be able to start all connected temperature controlling and temperature-monitoring equipment[9];
- be equipped with automatic mains failure start-up and automatic shut down when power is restored;
- have fuel tank capacity sufficient to cover a prolonged power outage.

Regularly test and service UPS equipment and generators. Maintain records to demonstrate compliance.

Reason: Loss prevention.

[8] UPS systems may be unnecessary in countries with a very reliable electricity supply. In smaller stores in countries where electricity is only available for a limited period each day, or is entirely absent, 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.

[9] The installed capacity of the UPS system can be minimized by fitting electronic controls which reduce compressor start-up loads.

3.9.2 Power failure contingency plan

Develop and maintain a contingency plan to protect TTSPPs in the event of a serious power failure. Alternative emergency cooling systems (e.g. liquid nitrogen or dry ice) are acceptable.

Reason: Loss prevention.

3.10 Building maintenance

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

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

4. Temperature-controlled storage

4.1 Normative references

- EN 60068-3 parts 5, 6, 7 and 11: *Environmental testing. Guidance. Confirmation of the performance of temperature chambers*
- IATA *Perishable Cargo Regulations Chapter 17.* 9th Edition, July 2009.
- USP <1079> *Good storage and shipping practices.*
- USP <1118> *Monitoring devices – time, temperature and humidity.*

4.2 Storage capacity of temperature-controlled stores

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

Reason: To avoid the risks associated with over-stocking and to ensure that good warehousing practices can be adopted (i.e. EEFO). Overstocking makes EEFO handling difficult or impossible and inhibits accurate physical stock counts.

4.3 Temperature-controlled storage

Ensure that TTSPPs 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

- 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;
- 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;
- connected to an uninterrupted power supply as described in clause 3.9.1;

- equipped with 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 access control system, as necessary;
- qualified as defined in clause 4.7.

Refrigerators and freezers

- purpose-designed for the storage of TTSPPs; household-style units are only acceptable for products that are unaffected by the temperature excursions which occur in such units;
- 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 and/or refrigeration failure;
- fitted with lockable doors or lids, or access control system, as necessary;
- qualified and/or tested as defined in clause 4.7.

Reason: To maintain labelled TTSPP storage temperatures during long-term storage.

4.4 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, as described in clause 3.6.2.
- Alternatively, but only if acceptable to the regulatory authority, bulk stocks of TTSPPs with high illicit-value may be stored in a securely locked section of a general temperature-controlled storage area.

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.

4.5 Temperature and humidity control and monitoring in storage

4.5.1 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;
- sensors accurate to ±0.5°C or better;
- sensors calibrated as described in clause 4.10.1;
- sensors located in areas where greatest variability in temperature is expected to occur in order to maximize available safe storage volume;

- 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.
- sensors independent of the temperature monitoring system.

4.5.2 Temperature monitoring

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

General requirements:

- sensors accurate to ±0.5°C or better;
- sensors calibrated as described in clause 4.10.1;
- 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.
- sensors positioned so as to be minimally affected by transient events such as door opening;
- thermometers, temperature traces or electronic temperature records manually checked at least twice a day, in the morning and evening, seven days a week.

Temperature-controlled rooms, cold rooms and freezer rooms

- provides a temperature 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;
- continues to operate independently in the event of a power failure[10].

Refrigerators and freezers

- as a minimum, provide a thermometer or maximum/minimum thermometer;
- preferably connect refrigerators and freezers to a multi-point 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[11];
- alternatively use battery-powered portable temperature monitoring devices with a minimum recording frequency of six times per hour;
- provide documentation for each appliance which can be stored and accessed.

Reason: To maintain labelled TTSPP temperatures during long-term storage.

4.5.3 Humidity control

Provide humidity control in temperature-controlled rooms that are used to store TTSPPs which are adversely affected by high relative humidity and are not sufficiently protected by packaging.

4.5.4 Humidity monitoring

Provide humidity monitoring systems and devices in temperature-controlled rooms that are used to store TTSPPs which are adversely affected by high relative humidity

[10] Where there is no UPS, the autonomy period for the device should be matched to the maximum length of anticipated power outages.

[11] *Ibid.*

and are not sufficiently protected by packaging. Systems and devices should comply with the following minimum requirements:

- sensors accurate to ±5% RH;
- sensors calibrated as 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.
- continues to operate independently in the event of a power failure[12].

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Reason: To maintain labelled TTSPP humidity conditions during long-term storage.

4.6 Alarm systems

4.6.1 Temperature alarms

Provide temperature alarm systems for temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPPs. Systems should 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.

Ensure that alarm sensors monitor the same medium (air or product) as the temperature alarm system.

Reason: Loss prevention.

4.6.2 Humidity alarms

Provide humidity alarm systems for temperature-controlled rooms, used to store TTSPPs that are sensitive to moisture and are not sufficiently protected by

[12] Where there is no UPS, the autonomy period for the device should be matched to the maximum length of anticipated power outages.

packaging. Systems and devices should comply with the following minimum requirements:

- sensors accurate to ±5% 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);
- 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.

Reason: Loss prevention.

4.7 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 when fully loaded;
- 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. Consider the need for re-qualification whenever temperature and/or humidity monitoring shows unexplained variability that is greater than normal.

Qualification may not be required for off-the-shelf equipment that has 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 to which the equipment will be exposed during operation.

Reason: To ensure that labelled TTSPP temperatures can be maintained during long-term storage and that the facility can demonstrate to the regulatory authorities and other interested parties that due diligence has been carried out.

4.8 Cleanliness of temperature-controlled stores

Implement a cleaning and decontamination programme 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.

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

4.9 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 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.

Reason: Loss prevention.

4.10 Calibration and verification of control and monitoring devices

4.10.1 Calibration of temperature control and monitoring devices

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

4.10.2 Calibration of humidity control and monitoring devices

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

4.10.3 Alarm equipment verification

Check functionality of temperature and humidity alarms at least once a year at the designated set points.

Maintain records to demonstrate compliance.

Reason: To ensure that labelled TTSPP storage temperatures and humidity control can be maintained during long-term storage and that the store can demonstrate to the regulatory authorities and other interested parties that due diligence has been carried out.

5. Materials handling

5.1 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.

6. Transport and delivery

6.1 Normative references

- Directive 94/62/EC. *European Parliament and Council Directive of 20 December 1994 on packaging and packaging waste.*1994.
- 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 Chapter 17,* 9th Edition, July 2009.
- *Isothermal and refrigerating containers for health products – Thermal performance qualification method.*
- *Practical guide – Cold chain for drugs.*
- 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.*

6.2 Product stability profiles

Transport TTSPPs 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.

Reason: Protection of TTSPPs against damage.

6.3 Transport route profiling and qualification

Profile and qualify transport routes:

- Select the most suitable methods for protecting TTSPPs against anticipated ambient temperature and humidity conditions encountered throughout the year.

- Use suitable methods, including published standards, weather data, laboratory tests and field tests to select suitable transport equipment and shipping containers.

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 the regulatory authorities and other interested parties.

6.4 Temperature-controlled transport

6.4.1 Air and sea transport

Ensure that any carrier contracted to transport TTSPPs by air or by sea operates under the terms of a formal Service Level Agreement drawn up between the parties.

Reason: To ensure that the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product and that compliance can be demonstrated to the contracting organization, the regulatory authorities and other interested parties.

6.4.2 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 Service Level Agreement drawn up between the parties.

Reason: To ensure that the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product and that compliance can be demonstrated to the contracting organization, the regulatory authorities and other interested parties.

6.4.3 Temperature-controlled road vehicles generally

Ensure that temperature-controlled road vehicles used for the transport of TTSPPs 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 TTSPPs 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 lockable doors.
- qualified as defined in clauses 6.6.1 and 6.6.2;

Carry out regular calibration and maintenance and keep records to demonstrate compliance.

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 the regulatory authorities and other interested parties.

6.4.4 Transport of controlled TTSPPs and TTSPPs with high illicit value

Ensure that controlled TTSPPs and TTSPPs with high illicit value are transported in the following manner:

- Transport practices comply with all relevant local 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.
- Contents are not indicated on outer packaging.
- 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 GPS devices located in the vehicle and/or hidden in the product.

Reason: To prevent theft and misappropriation of this category of TTSPP and to ensure the security and safety of the driver.

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6.5 Temperature and humidity control and monitoring during transit

6.5.1 Temperature control in temperature-controlled road vehicles

Provide thermostatic temperature control systems for all temperature-controlled vehicles used to transport TTSPPs. 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 8.6;
- sensors accurate to ±0.5°C;
- sensors calibrated as section 6.7.1;
- sensors located to control worst-case temperatures in order to maximize available safe storage volume;
- sensors positioned so as to be minimally affected by transient events such as door opening;
- sensors independent of the temperature monitoring system.

6.5.2 Temperature monitoring in temperature-controlled road vehicles

Provide air and/or load temperature monitoring systems and devices for vehicles used to transport TTSPPs. Systems and devices should comply with the following minimum requirements:

- sensors accurate to ±0.5°C;
- sensors calibrated as clause 6.7.2;
- sensors located to monitor worst-case temperatures 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 temperature record with a minimum recording frequency of six times per hour for each sensor position[13];
- provides documentation which can be stored and accessed.

[13] Recording frequency should take account of the storage capacity of the data logger and the expected transport period.

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

6.5.3 Humidity monitoring in temperature-controlled road vehicles

Preferably provide humidity monitoring systems and devices for temperature-controlled vehicles which are used to transport TTSPPs that are sensitive to moisture and are not sufficiently protected by packaging. Systems and devices should comply with the following minimum requirements:

- sensors accurate to ±5%RH;
- sensors calibrated as 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.
- provides a humidity record with a minimum recording frequency of six times per hour for each sensor position;
- provides documentation which can be stored and accessed.

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

6.5.4 Temperature monitoring in passive and active shipping containers

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.

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 the regulatory authorities and other interested parties.

6.6 Qualification of temperature-controlled road vehicles

Where temperature-controlled vehicles are directly owned and/or operated, qualify each vehicle before it becomes operational. The qualification procedure should:

- demonstrate the air temperature distribution 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;
- where products are being transported that are sensitive to moisture and are not sufficiently protected by packaging, demonstrate the humidity distribution throughout the temperature-controlled compartment for commonly used load layouts;
- 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.

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

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 the regulatory authorities and other interested parties.

6.7 Calibration and verification of transport monitoring devices

6.7.1 Calibration of transport temperature control devices

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

6.7.2 Calibration of transport temperature monitoring devices

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

6.7.3 Calibration of transport humidity monitoring devices

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

6.7.4 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.

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 the regulatory authorities and other interested parties.

6.8 Shipping containers

6.8.1 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;
- can be closed in a manner that allows the recipient of the consignment to establish that the boxes have not been tampered with during transport.

Reason: Quality assurance and safety.

6.8.2 Un-insulated containers

Ensure that un-insulated containers are correctly used in a manner which protects their contents:

- Transport un-insulated 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 TTSPP within the product's stability profile as stated by the product manufacturer and/or to maintain the TTSPP within the transit temperature

specification requirements specified by the regulatory authorities at both the sending and receiving locations.

Reason: Quality assurance and safety.

6.8.3 Qualification of insulated passive containers

Qualify insulated passive containers, including any and all necessary ancillary packaging such as temperature stabilising 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 TTSPP 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.

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 the regulatory authorities and other interested parties.

6.8.4 Qualification of active containers

Qualify active containers:

- Ensure that the container is capable of maintaining the TTSPP 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.

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 the regulatory authorities and other interested parties.

6.9 Shipping container packing

Pack TTSPP shipping containers to:

- 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 whilst 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 micro-organisms 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;
- ensure that packages containing dangerous goods (including dry ice) are labelled in compliance with relevant transport regulations and requirements.

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 the regulatory authorities and other interested parties.

6.10 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 clause 3.3.1.
- 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.
- Ensure that patients receiving TTSPP deliveries are given clear advice on correct product storage before use.

Reason: To maintain TTSPP quality during transport.

6.11 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.
- 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.

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

6.12 Transport of returned and recalled TTSPPs

6.12.1 Transport of returned TTSPPs

Ensure that that returned TTSPPs 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.

- 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.

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

6.12.2 Transport 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 as clause 7.5.3.

7. Labelling

7.1 Normative references

- *IATA Perishable Cargo Regulations Chapter 17 9th Edition, July 2009. Clauses 17.10.5 and 17.10.6.*

7.2 Labelling

7.2.1 Labelling 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.
- indicate the appropriate temperature and humidity ranges within which the product is to be transported and/or stored.

7.2.2 Labelling air-freighted shipments

In cases where TTSPPs are to be air-freighted, label packaging using the standard IATA *Time and Temperature-sensitive* symbol. Apply the label to the outer surface of individual shipping packages, overpacks or bulk containers.

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

8. Stock management

8.1 Stock control systems

8.1.1 General stock control systems and procedures

TTSPP stock control systems and procedures should meet the following minimum requirements:

- Provide security-enabled access control designed to ensure that the system cannot be accessed by unauthorized persons.
- Record all receipts and dispatches.
- Record batch numbers and expiry dates.

- Record short-dated and expired products.
- Record product status (e.g. released, quarantined, hold, reject, etc.).
- Record all product returns, recalls, withdrawals, damage and disposals.
- Manage the issue of products in EEFO order.
- Take regularly 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 conducted at least twice a year.

Reason: To ensure that accurate and complete stock records are kept at all times.

8.1.2 Stock control procedures for controlled and hazardous TTSPPs

In addition to the requirements set out in clause 7.1.1, implement the following procedures:

- 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 local legislation and regulations. Retain product transaction/delivery records for at least the minimum time period required by local regulations.

Reason: To ensure that accurate and complete stock records are kept at all times and to satisfy the requirements of the regulatory authorities.

8.2 Goods incoming

8.2.1 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; 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.

8.2.2 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.

- 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.

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.

8.3 Goods outgoing (external deliveries)

8.3.1 Management of outgoing goods

Implement outgoing goods procedures to ensure that:

- Transport vehicle conformity, including conformity with SLA or 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 product-based time-temperature exposure indicators demonstrate 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.

8.3.2 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. A suitable delivery report from the carrier is an acceptable alternative.
- Take appropriate action in the event of returns, recalls or complaints.

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.

8.4 Product complaint procedures

Manage product complaints as follows:

- If a product defect is discovered or suspected in a batch of TTSPPs, determine whether other batches are affected and whether a product recall is required.
- Where complaints or defects relate to a product or its packaging, immediately notify the holder of the marketing authorisation 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 measure to prevent a recurrence.
- Record all complaints and the remedial actions taken. Monitor and analyse trends in the complaint records.

Reason: Protection of the public and the reputation of the supplying organization.

8.5 Product return, recall, withdrawal, and disposal procedures

8.5.1 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 authorisation regarding handling and/or disposal of the returned TTSPP.
- 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 TTSPPs that have been exposed to incorrect storage and/or transport temperatures and mark for disposal.
- Maintain records of all returned TTSPPs.

Reason: Protection of the public.

8.5.2 Recall procedures

Manage product recalls as follows:

- Conduct urgent and non-urgent TTSPP recalls in accordance with an agreed emergency plan.
- Notify the local regulatory authority(ies).
- Notify overseas regulatory counterparts where the product has been exported.
- Notify all affected customers as applicable.
- Quarantine any remaining inventory of recalled TTSPPs and mark for disposal.
- Maintain records of all TTSPP recalls, including reconciliation of quantity sold, quantity returned, quantity remaining, quantity consumed, etc).

Reason: Protection of the public and conformity with regulatory requirements.

8.5.3 Disposal procedures

Manage product disposals as follows:

- Ensure that rejected and/or recalled/withdrawn TTSPPs cannot be used, released or cause contamination to other products. Store separately from other products until they are destroyed or returned to the supplier.
- Safely dispose of rejected and/or recalled/withdrawn products in accordance with local regulations, including where relevant, regulations covering the disposal of hazardous and controlled drugs.
- Maintain disposal records.

Reason: Protection of the public and the environment.

8.6 Counterfeit product procedures

8.6.1 Counterfeit products

Implement systems for identifying and managing counterfeit products found in the supply chain as follows:

- Physically segregate any counterfeit TTSPPs found in the supply chain and store securely until legal investigations are complete.
- Label them clearly as 'Not for sale' or other similar phrase.
- Immediately notify the regulatory authority(ies), the police, and the holder of the marketing authorisation of the original product.
- Cooperate with regulatory authorities to assist with investigating the source of counterfeit products and implement appropriate remedial action(s).
- Document the decision-making process for disposal of counterfeit TTSPPs and make these records available to the relevant authorities.

Reason: Protection of the public, protection of legitimate suppliers and manufacturers and conformity with regulatory requirements.

8.7 Traceability/ stock tracking

8.7.1 Traceability

Ensure that stock and distribution records enable traceability of TTSPPs from the point of supply to the end user/patient. Traceability should include records of the temperature exposure of the product during internal shipping and storage. Monitor, record, and investigate discrepancies.

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

9. General procedures and record keeping

9.1 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;
- vehicle breakdown during transport of TTSPPs.

Prepare action plans to deal with products subjected to temperature excursions. Ensure that responsible staff know, and have rehearsed, the appropriate actions to be taken in the event of the identified emergency scenarios.

Reason: Loss prevention.

9.2 General record keeping

9.2.1 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 unauthorised access;
- signed and dated by authorised persons and not changed without due authorisation;

Computer records must be:

- logically filed for easy identification and retrieval;
- kept secure and protected against unauthorised access;
- manually signed, dated and scanned or electronically signed and dated by authorised persons and not changed without due authorisation;
- regularly backed up and archived on a secure server.

9.2.2 Content of records

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

- Product arrival status.
- Temperature and humidity records including records of excursions outside labelled storage and/or transit temperature specification conditions.
- General TTSP 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.
- Counterfeit product reports, where relevant.

Maintain all records in accordance with local legislation and regulations..

9.2.3 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.

Reason: Internal quality control, transparency and external inspection by the regulatory authorities and other interested parties.

9.3 Temperature and humidity records

9.3.1 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.

9.3.2 Humidity records

Where applicable, monitor and record humidity levels in all temperature-controlled rooms as follows:

- Record humidity at least twice every 24 hours and 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, or as long as required by national legislation.

Reason: Internal quality assurance and availability of records for review by the regulatory authorities and other interested parties.

10. Environmental management

10.1 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.

10.2 Environmental management of refrigeration equipment

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);
- 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.

Reason: Compliance with international protocols and accords on climate change and environmental protection.

11. Quality management

11.1 Normative references

- ICH, 2005: *ICH Harmonised 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*

11.2 Organizational structure

Establish, document and maintain an organizational structure for the TTSPP storage and shipping and distribution operations which clearly identifies all key management responsibilities, and the individuals accountable.

Reason: Quality management.

11.3 Quality systems

11.3.1 Quality system

Establish, document and maintain a quality system for the management of TTSPPs 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) programme;
- 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;
- self-inspection programme;

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

Reason: Quality assurance.

11.3.2 Self inspections

Conduct regular self-inspections to ensure continuing compliance with quality management standards Good Storage Practice (GSP) and Good Distribution Practices (GDP); record results.

Reason: To demonstrate compliance with adopted quality management standards.

11.4 Management of documents and SOPs

11.4.1 Standard operating procedures (SOPs)

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

- Security, including management of controlled and hazardous TTSPPs.
- Safe handling of TTSPPs.
- 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 fulfilment, packing, etc.).
- 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.
- Temperature-controlled packaging and route qualification.
- Temperature-controlled vehicle operation.
- Emergency response procedures.
- Environmental management.

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

Reason: Quality management and staff training.

11.5 Document change control

Ensure that all quality manuals, standard operating procedures and the like 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;
- withdrawn when superseded.

Withdraw superseded documents and retain record copies for document history files.

Reason: Good quality management practice.

12. Personnel/ training

12.1 Normative references

- IATA *Perishable Cargo Regulations Chapter 17*. 9th Edition, July 2009

12.2 Training

12.2.1 General training

Provide regular and systematic training for all relevant personnel responsible for storage, loading and unloading areas used for non-hazardous TTSPPs, covering the following:

- applicable pharmaceutical legislation and regulations;
- standard operating procedures and safety issues;
- response to emergencies.

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

Reason: To ensure that all relevant personnel are competent to carry out their duties.

12.2.2 Specialist training

In addition to the training described in clause 12.2.1, provide regular and systematic additional training for relevant personnel responsible for storage, loading and unloading used for controlled or hazardous TTSPPs. Training should cover the following:

- applicable legislation and regulations;
- security and safety risks;
- 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. Maintain individual training records to demonstrate compliance.

Reason: To ensure that all relevant personnel are competent to handle controlled or hazardous TTSPPs.

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Annex 3 – Task force membership

Name	Organization	Category	Country
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Michael Eakins	USP Packaging and Storage Expert Committee, USP, USA	Regulatory	USA
Juliman Fuad	Bio Farma / Indonesia	Manufacturer	Indonesia
Andreas Giger	Berlinger	Temperature monitoring	Switzerland
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Revision history

Date	Change summary	Reason for change	Approved
01.10.2009	V1b: Note on document status added	ECBS requirement	
28.04.2010	V2: Incorporating further review comments		
11.05.2010	V2b: Further revisions and reorganization		

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