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Temperature-controlled transport operations by road and by air

Technical supplement to
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Annex 9: Model guidance for the storage and transport of time and temperature–sensitive pharmaceutical products

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Abbreviations

AWB	Air Way Bill
CI	Chemical Indicator
CCP	Critical Control Point
CRT	Controlled Room Temperature
ETI	Electronic Temperature Integrator
EDLM	Electronic Data Logging Monitor
IATA	International Air Transport Association
NOTOC	Notification to Captain
PDA	Parenteral Drug Association
SLA	Service Level Agreement
SOP	Standard Operating Procedure
TTI	Time-Temperature Integrator
TTSPP	Time- and Temperature-Sensitive Pharmaceutical Product
ULD	Unit Load Device
URS	User Requirements Specification

Glossary

3PL: Third party logistics provider: a firm that provides service to its customers of outsourced (or "third party") logistics services for part, or all of their supply chain management functions.

4PL: Fourth party logistics provider: a general contractor who manages other 3PLs, truckers, forwarders, custom house agents, and others, essentially taking responsibility for a complete logistics process for the customer.

Active systems: Externally powered or on-board 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).

Advanced Phase Change Materials (PCMs): Temperature stabilizing media (sometimes referred to as refrigerants), chemically engineered so that their latent heat of fusion occurs at a temperature other than zero ° C, phasing from one state of matter to another (i.e. liquid to solid) at a pre-formulated temperature. Such materials are typically comprised of oils, salts, or paraffin.

Ancillary packaging components: Packaging elements used to protect the TTSPP and support or enhance performance of the completed package. This may include retainers, dunnage, secondary protective packaging, and temperature data logging devices.

Chemical indicators: (also called markers or phase-change indicators), are generally impregnated onto a paperboard substrate. These indicators, sometimes referred to as critical temperature indicators, are based on a phase change or chemical reaction that occurs as a function of temperature. Examples include liquid crystals, waxes, polymers, and lacquers that change phase, and thereby their appearance, as a function of temperature. Chemical temperature threshold indicators are irreversible and are suitable for high or low temperatures. Temperature threshold indicators show a response and typically are single-use devices. These indicators provide a signal only when exposed to temperatures higher than (ascending indicator) or lower than (descending indicator) a predetermined threshold temperature.

Coolant: Ice, water, water-based gel, phase-change material, dry ice, or other substance, typically encapsulated in a rigid or flexible plastic container, used to maintain a pre-defined temperature range inside a passive container during transport operations.

Critical Control Point (CCP): A step or procedure at which controls or checks can be applied to prevent or reduce a hazard or risk to and acceptable or critical level. In the context of distribution and handling of time and temperature-sensitive healthcare products, critical control points are typically defined for those activities where time and temperature abuse may occur or where critical processes that can affect the performance of the packaging solution or containment system are at risk.

Electronic Data Integrator (EDI): A hybrid electronic instrument intelligently programmed like an Electronic Temperature Indicator (ETI) with the report/data producing capabilities of an Electronic Data Logging Monitor (EDLM) that combines the features and functions of a Go/No-Go device (like and indicator) with the record retention and data tracking of an EDLM but with greater granularity and data management

flexibility. It uses pre-programmed temperature threshold intelligence to integrate post-analytic functional steps that are typically performed by trained personnel.

Electronic Data Logging Monitor (EDLM): A small portable device that measures and stores temperature at a pre-determined time intervals by means of an electronic sensor. They have programmable alarm capabilities, integrated displays, and can create reports and graphs which may be permanently stored, shared and analysed via proprietary hardware, software, desktop application or through hosted databases.

Electronic Temperature Indicator (ETI): A compact, portable device that measures, temperature over time by means of a built-in sensor. They come in a wide range of forms, features, configurations, cost and levels of performance. Their composition consists of four basic components: a thermistor sensor, a microprocessor, a memory chip, and power source (lithium battery).

Electronic temperature monitoring and event logger system: System for recording and reporting air and/or product temperatures, with optional facilities for recording and reporting specific events such as door-opening or defrost cycles, and for issuing alarms. Such systems may be user-programmable and may also be remotely monitored via a satellite link.

External distribution: Transport of TTSPPs through various steps in the customer's supply chain (i.e. transport from a pharmaceutical manufacturer's distribution centre, to commercial customers (including wholesalers, retailers and buying groups), to clinical facilities or direct to the patient). Contrast with *internal distribution.*

Internal distribution: Transport of a TTSPP within a pharmaceutical manufacturer's internal supply chain (i.e. all internal transport from the manufacturing plant to the packaging plant and onwards to warehouses and distribution centres). Contrast with *external distribution.*

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. Medical devices are not included[1].

Refrigerated vehicle: Road transport vehicle such as a van, truck or semi-trailers whose isolated thermostatically controlled cargo compartment is maintained at a temperature different (lower or higher) than that of the external ambient conditions. The environment inside the cargo compartment may be *temperature-controlled* or *temperature-modified.*

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.

[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*.

Service Level Agreement (SLA): 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[2].

Shipping system: All components constituting a completed package including: the outer shipping container, all internal ancillary packaging components and temperature stabilizing medium.

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.

Temperature excursion: An 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.

Temperature stabilizing medium: Ice or gel packs; gel bricks, bottles or pouches; cool water or warm water packs, phase change materials, dry ice, rapid evaporation media which limit exposure of packed product to excessively high or low temperatures during transport: also referred to as refrigerants or coolants.

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 predefined limits.

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.

Time-Temperature Integrators (TTI's): Are generally chemically impregnated onto a pulp or paperboard substrate. Their reaction rate or diffusion process is used to estimate a temperature equivalent integrated over time. Thus, TTIs provide a measure of accumulated heat rather than instantaneous temperature such as a spike or critical threshold (see Chemical Indicators). The reactions are irreversible – once a colour change, colour development, or diffusion process has taken place, exposure to low temperatures will not restore the indicator to its original state. They change colour, or are marked by a hue progression in intensity (generally from light to dark) in response to cumulative

[2] Definition from IATA. *2013/2014 Perishable Cargo Regulations (ePCR) & Temperature Control Regulations (eTCR)*

changes in temperature, such as heat, at a rate dependent on the Arrhenius Equation. A TTI accumulates all of the temperature conditions experienced by the product to which it is affixed. The colour development can be customized based on the known stability of the product, and in much the same way that most biologics and pharmaceuticals degrade when exposed to heat - faster at higher temperatures, and slower at lower temperatures.

Unit Load Device (ULD): A container used for consolidating and transporting cargo aboard aircraft. They are generally made of aluminium and / or fibreglass and configured to fit the geometry of an aircraft and are considered part of the aircraft frame. Large Active Systems fall into the category of ULD. There are two basic sizes classified by the airline industry: LD-3 and LD-9.

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

Work instruction: Describes *how* to complete a specific task. Contrast with an SOP which describes *who* (title or department) should carry out a series of tasks, and in what sequence.

[3] PDA Technical Report No. 39: *Guidance for Temperature Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment*, 2007.

1. Introduction

This technical supplement has been written to amplify the recommendations given in Section 6.4 and 6.5 of WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*[4]. It provides guidance on how to condition, load and handle equipment used to transport TTSPPs in order to maintain these products with a pre-defined operating temperature range. The supplement covers refrigerated and temperature-controlled transport vehicles and active and passive shipping containers for road and air transport operations. Fixed storage systems, such as cold rooms and refrigerators, are outside the scope of this document.

The following Technical Supplements are also relevant:

- *Qualification of shipping containers.*
- *Qualification of temperature-controlled road vehicles.*
- *Temperature and humidity monitoring systems for transport operations.*
- *Transport route profiling qualification.*

1.1 Requirements

Packaging systems should be qualified before use. Generally speaking, the shipper is responsible for ensuring product temperature compliance during transport.

1.2 Objectives

The objective of the Technical Supplement is to:

- Provide a general technical introduction to the active and passive packaging and transport systems used for distributing TTSPPs.
- Describe how to pack temperature controlled products correctly in active and passive systems and how to manage their transit through the transport environment.
- Describe the correct use of the various types of temperature and humidity monitoring device.
- Describe the documentary evidence that should be supplied to regulatory authorities and other interested parties so that quality assurance and regulatory compliance can be demonstrated and maintained.

1.3 Target readership

This technical supplement is intended for all those responsible for the transport of TTSPPs through the supply chain from one fixed storage point to another.

Staff responsible for transport operations need to understand the importance of pharmaceutical product temperature stability, have a sound working knowledge of applicable logistics and transport methodologies within their organizations, and they should understand the basic concepts of packaging thermodynamics and good

[4] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf

documentation practice. They should have a good knowledge of the various types of temperature monitoring device used in the transport environment, together with their strengths, weaknesses and appropriate uses. They must also be able to train and supervise junior staff so that they are able to carry out the tasks described below in a reliable and consistent manner.

2. Guidance

This section describes the processes that need to be followed to ensure safe transport of TTSPPs by road and air. These two transport modes involve similar processes. The options available for ocean transport are not covered here because this transport mode has its own unique requirements. For general guidance on importation and port clearance procedures readers should also refer to Chapter 24 of MDS-3: *Managing Access to Medicines and other Health Technologies – Importation and port clearing* and to the IATA document: *Temperature Control Regulations: The Global Standard for the Safe Transportation of Healthcare Products by Air.*

2.1 Associated materials and equipment

The physical components of a quality-assured temperature-controlled transport system are the active and passive packaging systems, described below, in which products are placed during transport. Temperature monitoring devices are also a key component. The specific characteristics and uses of these devices are described in the companion Technical Supplement: *Temperature and humidity monitoring systems for transport operations.*

2.2 Available shipping systems

Temperature control during ground air or ocean transport can be maintained using either active or passive shipping systems, as described below.

2.2.1 Refrigerated vehicles – temperature-controlled

This category includes vans, rigid trucks and semi-trailers that have an insulated thermostatically controlled cargo compartment and a dedicated refrigeration unit capable of maintaining the labelled temperature range of the products being transported. Vans and small rigid trucks typically have refrigeration units powered directly by the vehicle's engine. Larger rigid vehicles and semi-trailers have independent diesel-powered refrigeration units. Both types may also have electrical back-up so that they can be mains-powered whilst parked. All refrigerated vehicles should be equipped with an on-board electronic temperature monitoring and event logger system.

Refrigerated vehicles must be properly qualified for their designated operating environment. They should only be used in operating environments that are able to manage the equipment, and over roads which will not damage the vehicles. Refer to Technical Supplement: *Qualification of temperature-controlled road vehicles.*

2.2.2 Refrigerated vehicles – temperature-modified

These are similar to temperature-controlled refrigerated vehicles, except that the vehicle itself simply moderates the ambient temperature, either by heating or cooling. The transported product is generally packed in a qualified passive shipping system designed to keep it within the labelled temperature range. The temperature-modified environment in the vehicle serves to extend the autonomy of the passive shipping system and protect the product from temperature extremes. Care must be taken not to subject the packages to refrigerated temperatures (e.g. +2.0°C to +8.0°C) for extended periods because this risks freezing the package contents. Ideally, operators should avoid exposure of active and passive packaging to temperatures below +15.0°C. In order to ensure this, temperature-

modified vehicles should preferably be equipped with an on-board electronic temperature monitoring and event logger system.

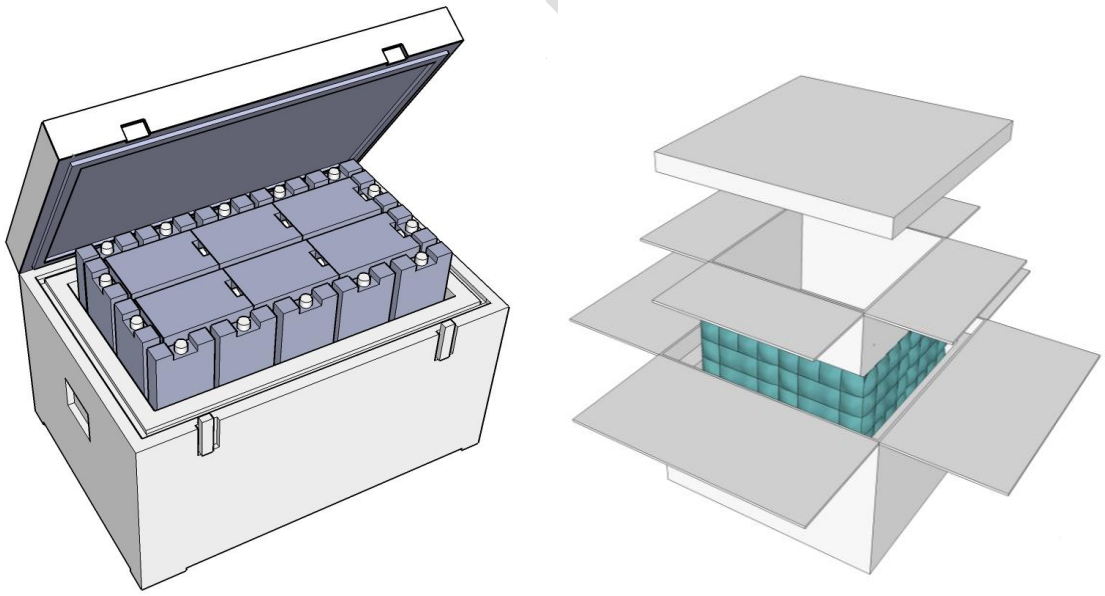
The recommendations on use described above for temperature-controlled refrigerated vehicles also apply.

2.2.3 Passive shipping systems

A particular advantage of passive systems in resource-constrained settings is that safe transport of TTSPPs can reliably be provided over poor roads. They can also be used for air transport. A properly qualified passive shipping system can be used to maintain effective temperature control of the drug product at ambient transport temperatures. However these systems should only be used after the route and container has been qualified – see Technical Supplements: *Transport Route Profile Qualification* and *Qualification of shipping containers.*

Passive shipping systems consist of a combination of insulated material and temperature stabilizing media. When correctly configured, such a combination can keep the internal contents of the package within a specified temperature range for a pre-defined period of transport, without reliance on mechanical assistance. The packages are sealed in specific configurations and do not rely on any further human or mechanical intervention to perform to a specific level during transport. However, they have a predefined transport life and consequently delivery must always be achieved within this period[5]. Figure 1 shows an example of both a reusable and a single-use passive container.

Figure 1 – Generic passive containers with coolant packs



Reusable container | Disposable insulated carton

The impact-resistant outer layer of disposable packaging is typically made of corrugated fibreboard which protects the insulated lining. Reusable containers have a durable outer shell, insulating core and inner liner designed to last for multiple journeys. In both cases, thermal control is provided by coolants which are chosen to maintain a specific

[5] O'Donnell, K., Wright, A. *Good Distribution Practices by Air, Road & Ocean Workbook and Resource Guide*, 2013.

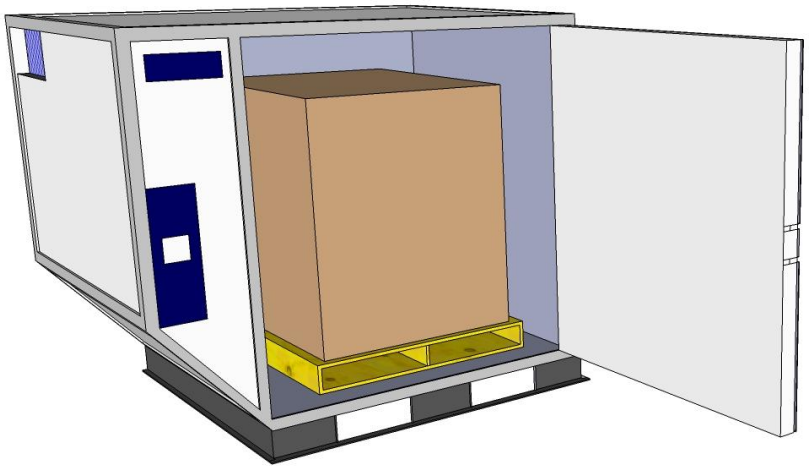
temperature range inside the package; depending on the type of container these may either be disposable or reusable. The packaging system is completed by other ancillary packaging components used as separators, dividers or dunnage.

The temperature of the product within the package is maintained by applying the physics of conduction and convection in conjunction with the stored latent heat of fusion from the refrigerant. All passive packaging systems contain a finite amount of refrigerant energy. More sophisticated packaging uses advanced phase change materials (PCMs) instead of water-based gel packs or simple water-packs.

2.2.4 Active shipping systems for air transport

The typical active shipping system is a dedicated portable container. They come in two types: systems with cooling only, and systems with both heating and cooling[6]. The temperature stabilizing medium in active shipping systems comprise dry ice (cooling types only) or use phase change materials (heating and cooling types) as a means to provide temperature control; alternatively compressor-driven cooling systems are also widely used. These containers are either powered by on-board batteries, or use an external electrical source to run on-board compressors or heat pumps. Thermostatic control is used to activate the cooling or heating mechanism and circulating fans help to maintain temperature within specified limits around the enclosed product. Larger containers are generally leased from the manufacturer, or by an air or ocean carrier, or by a third party logistics service provider. Figure 2 shows an example.

Figure 2 – Active air transport container – type LD3



2.3 Quality agreements

A safe and reliable temperature-controlled transport operation starts with a comprehensive User Requirements Specification, informed by a thorough risk assessment exercise. This can be used as a basis for contracting out services via a Service Level Agreement, or for managing an in-house operation. However, the service is provided, suitable SOPs, standard check lists and associated work instructions must be developed and used to control each shipment.

[6] Heat-only units are also available, but unlikely to be relevant for TTSPP transport.

2.3.1 User Requirements Specification

The shipper is responsible for ensuring that the packaging and the mode(s) of transport used to distribute TTSPPs are capable of maintaining the products within their specified temperature and humidity ranges. Accordingly, the detailed requirements for each type of transport operation must be fully defined and suitable transport service providers identified and appointed. The correct way to do this is to draw up a User Requirements Specification (URS). This document should clearly define the following:

- The temperature and humidity parameters that must be maintained for each product or product type; these parameters are determined by the product label, or when acceptable, the manufacturer's stability data;
- The transport mode and/or vehicles to be used;
- The required level of service;
- Acceptable levels of risk to product and performance;
- The types of packaging;
- The types of temperature and humidity monitoring devices to be employed and the acceptable level of accuracy of these devices;
- Specific service actions such as go/no-go decision-making in the event of a temperature excursion event, or more complex analytical data gathering and reporting requirements.

The URS can be used as a basis for developing SOPs and work instructions for in-house transport operations, and/or a Service Level Agreement for contracted-out transport services.

2.3.2 Service Level Agreements (SLAs)

Shippers and other transport service provider stakeholders should operate under mutually agreed upon terms of an SLA, which i specifies the target and minimum levels of performance, service, operation or other attributes as set out in the URS. In-house transport services should be controlled with a similar level of rigour. An SLA should contain the following elements:

Introduction:

- Purpose and objective of the SLA;
- Parties to the agreement;
- Commencement date;
- Duration of the agreement;
- Definitions and glossary of terms.

Scope of work:

- Standard service(s);
- Non-standard service(s);
- Place of service, including collection and delivery locations;
- Changes to service.

Compensation:

- Fee tariff;
- Invoicing arrangements;
- Payment terms.

Performance monitoring and reporting:

- Managing changes in key personnel;
- Service benchmarks;
- Service monitoring and reporting mechanisms;
- Service review meetings.

Problem management:

- Support services;
- Problem identification;
- Problem escalation procedures.

Duties and responsibilities:

- Customer / client personnel, facilities, resources;
- Training for specialized equipment/tasks;
- Approvals.

Warrantees and remedial action:

- Allocation of responsibilities between the parties to the agreement;
- Liability;
- Resolution procedures and penalties for non-compliance.

2.4 Identifying and controlling risk

A key characteristic of transport operations is the number of 'touch-points', 'hand-offs' or process and service exchanges between the various organizations and individuals involved. The TTSPP product is at the greatest risk of improper handling during these exchanges. For this reason they are defined as Critical Control Points in the transport supply chain. Table 1 lists the actions that may need to be taken to reduce risk or hazard to an acceptable level at each of the key stages in an air freight operation – not all of these will be mandatory for every shipment and every shipping system.

Table 1 – Critical Control Point actions for air freight

Critical handling process	Type of risk control
Product preparation and conditioning at shipper's location	• Electronic temperature monitoring of storage facility. i.e. refrigerator, freezer, cold room, warehouse. Humidity monitoring where appropriate. • Defined conditioning and staging time specifications for packaging components – temperature and duration, compliant with DQ and OQ.
Product loading at shipper's location	• Defined process, check sheet • Application of IATA TTSPP label • Defined actions in the event of delays
Ground transport from shipper	• Use of refrigerated or temperature-controlled vehicle – Temperature defined and pre-conditioned before

Critical handling process	Type of risk control
location	loading. – Electronic temperature monitoring. Humidity monitoring where appropriate. • Serviceability checks on equipment • Defined actions in the event of delays
Warehousing (en route)	• Use of IATA Standard Acceptance Checklist for Time and Temperature Sensitive Healthcare Shipment • Temperature monitoring. Humidity monitoring where appropriate. • Availability of batteries, electrical connections or dry ice to maintain correct temperature of active containers • Availability of sub-zero, refrigerated or controlled room temperature storage when required • Defined storage instructions • Defined actions in the event of delays, and mishaps en route
Airport tarmac/apron	• Minimize time exposed to ambient temperatures • High priority ramp handling • Covered storage when transiting through multiple airports • Use of passive protection tools such as thermal blankets • Defined actions in the event of delays
Aircraft hold	• Avoid positioning near cargo door • Cargo hold temperatures maintained between +15.0°C and +25.0°C • NOTOC (notification to captain) defining cargo hold temperature setting or use of dry ice in active containers

Wherever temperatures are read and recorded, the record should be to a minimum of one decimal place.

The following sub-sections set out the content of the checklists needed to operate three distinct types of shipping system:

- refrigerated and temperature-controlled vehicles;
- passive shipping systems sent by road and air transport
- operations using both passive and active containers.

Each of the checklists follows the same sequence: pre-shipment actions; actions on the day of shipment at the point of origin; actions during transit; actions on the arrival day at the destination and, finally, post-shipment actions.

2.5 Managing refrigerated road shipments

Refrigerated and temperature-controlled transport services are often supplied by a third party service provider specializing in such transport. Alternatively, the service may be directly operated by a national public health system, a parastatal company, or by a public-private partnership (PPP). In all cases it is important that service providers conduct regular, periodic training of responsible personnel, whether directly employed or sub-contracted.

It is essential that the correct infrastructure is in place to support the operation of these specialized vehicles. Specifically, all regular drop-off points should have a compatible electrical connection to power the cooling unit, especially for smaller vehicles where the

refrigeration circuit is powered off the vehicle engine generator. This is critically important in settings that involve overnight stops. In instances where the refrigeration unit is powered solely by the vehicle's engine, the engine must remain running at all times to avoid interruptions in maintaining proper temperature.

Vehicles should be equipped with an integrated continuous temperature monitoring and data logging system. In addition retrievable temperature data logging devices should preferably also be packed with the shipped product[7].

The action sequence below is based on risk mitigation principles. Some steps may be omitted or modified, provided there is a technical justification for doing so.

Pre-shipment actions:

a. Arrange booking, pick-up time and location.
b. Obtain confirmation from the consignee to ship the product (e.g. purchase order or requisition).
c. Verify product dimensions and determine the type of container required.
d. Book the shipment with the prequalified and approved freight forwarder or transport service provider.
e. Specify temperature requirements.
f. Prepare shipping documentation and checklists.
g. Ensure that the designated vehicle is in good working order, that its service record is up-to-date and that the driver has carried out the relevant daily safety inspection.

Shipping day: actions at point of origin:

a. Confirm booking, pick-up time and location.
b. Pack the product in its correct tertiary package and attach temperature monitoring devices to suit the routing requirements. Keep product under proper storage conditions until the time of despatch.
c. Ensure that the vehicle is fully operational and that the cargo area is clean and odour-free.
d. Before loading, pre-condition the product and the refrigerated vehicle's cargo area to the required transport temperature. Keep loading door(s) closed until it is time to load the product
e. Ensure that the thermostatic controller on the transport vehicle is set to the required temperature and ensure that the temperature recording device(s) are operating properly.
f. Check that vehicle's refrigeration unit is operating properly and that the temperature has stabilized.. Drivers must ensure the correct temperature setting has been selected.
g. Load product without delay. Do not overload the vehicle. Allow for air circulation around all sides of the product. Properly block and brace the load, as shown in

[7] For details of suitable systems refer to Technical Supplement: *Temperature and humidity monitoring systems for transport operations.*

Annex 1, to avoid shifting during transit. Close door(s) and apply security seal and/or lock if required.

h. Whenever possible, ensure that the driver is able to supervise the loading process.

i. If the refrigeration unit has been operating on mains electric power during loading, make sure that engine-powered refrigeration system is operating correctly and that the temperature has stabilized within pre-defined limits before releasing.

j. Provide clear instructions to the driver covering the correct load temperature, handling and transport requirements.

k. Provide emergency contact information to the driver.

l. Ensure that all paperwork and checklists are completed by responsible parties.

Actions during transit:

a. Cooling units must remain active throughout the entire journey, including stops and rest periods[8].

b. Energy-saving modes/options of the cooling unit should not be used.

c. Vehicle payload doors must only be opened during loading and unloading and opening time must be kept to a minimum[9].

d. In order to avoid theft and tampering, only use secure parking areas.

e. Minimize the time when vehicle is unattended by the driver.

Arrival day: actions at destination point(s):

a. Ensure priority unloading.

b. Remove product from the vehicle and move it immediately to correct temperature-controlled storage conditions.

c. Retrieve temperature data from driver. Refer to the companion Technical Supplement: *Temperature and humidity monitoring systems for transport operations.*

d. Record temperature upon arrival. Communicate any deviations to the appropriate personnel.

e. When the product is received, the consignee should retrieve and deactivate the temperature monitors accompanying the shipment and read and download the data. *Note:* If temperature monitors are not packed with the product, the data from the on-board temperature recording system should be downloaded, or a print-out obtained from the driver and attached to the arrival forms.

f. Ensure all checklists and arrival forms are completed by the responsible parties.

Post shipment actions:

Forward completed checklists and completed arrival forms to appropriate personnel, including electronic temperature data files.

[8] At some border crossing points there may be restrictions on the running of engines due to defined maximum permissible noise levels (dB).
[9] Note that doors may have to be opened for customs inspection.

2.6 Managing passive container road shipments

Wherever possible, covered vehicles should be used for transporting passive containers so that shipments are not exposed to the sun or to the elements. The action sequence below is based on risk mitigation principles. Some steps may be omitted or modified, provided there is a technical justification for doing so.

Pre-shipment actions:

a. Ensure that there are sufficient quantities of all packaging components to accommodate the shipment on the shipping day.

b. Ensure that all components have been conditioned to the correct temperature (i.e. temperature stabilizing media, whether frozen or refrigerated).

c. Ensure that the designated vehicle is in good working order, that its service record is up-to-date and that the driver has carried out the relevant daily safety inspection.

Shipping day: actions at point of origin:

a. Prepare and pack product in its designated secondary or ancillary packaging..

b. Assemble the passive shipping system and pack and load the product in accordance with approved site procedures.

c. Add temperature data loggers or temperature indicators if required. Place in close proximity to the product. Do not allow them to come in contact with temperature stabilizing media.

d. Ensure that all paperwork and checklists are completed by the responsible parties.

Actions during transit:

a. Vehicles should be parked in a secured parking area during rest stops; wherever possible, vehicles should also be parked in the shade;

b. Containers must not be opened during transit.

Arrival day: actions at destination:

a. Open packaging, remove product from its passive shipping system and move it immediately to correct temperature-controlled storage conditions.
b. Retrieve and deactivate temperature monitors for data retrieval.
c. Ensure all checklists and arrival forms are completed by responsible parties.

Post shipment actions:

a. Forward completed checklists to appropriate personnel, including electronic temperature data files.
b. Process packaging by disposal, reconditioning or reuse as appropriate.

2.7 Introduction to air transport

Because of time considerations, lack of infrastructure, and geographical obstacles, air transport is frequently the mode of choice for long distance transport for TTSPP's, both between and within countries. The International Air Transport Association's *Perishable Cargo Regulations* and *Temperature Control Regulations* is the industry's framework for meeting Good Distribution Practices (GDP)[10]. The purpose of the regulations is to:

- Describe packaging/systems used in drug product distribution;
- Identify potential risks to product quality;
- Recommend Critical Control Points to reduce these risks;
- Describe operating agreements such as SLA's or Quality Agreements;
- Define and delineate Quality Management System requirements;
- Define labelling requirements;
- Recommend handling procedures.

Many air carriers offer 'branded services' with defined procedures based on GDP to meet the specific needs of TTSPPs. Any variation or deviation from such a branded service should be defined and negotiated beforehand in a specific SOP.

In order to minimize risk, shippers should always collaborate with the air carrier, either directly or through the designated freight forwarding agent. It is essential to do this in order to define and agree the service level needed to meet the shipper's requirements.

Temperature control within the cargo holds of most aircraft is limited and wide variations can occur throughout the hold; these variations depend upon placement, location, time at altitude, and the duration of the flight. However, the greatest and most frequent vulnerability to temperature exposure occurs on the airport tarmac when goods are exposed to the elements before aircraft loading, or during unloading. Every precaution should be made to limit this exposure. Shippers are encouraged to work with their air service suppliers to minimize tarmac times.

[10] GDP requirements embrace the activities of pharmaceutical manufacturers, shippers, 3PLs, 4PLs, cargo agents, freight forwarders, independent air carriers, airlines, packagers and active solution platform providers, warehousing agents and ground handlers.

2.7.1 Types of air carrier

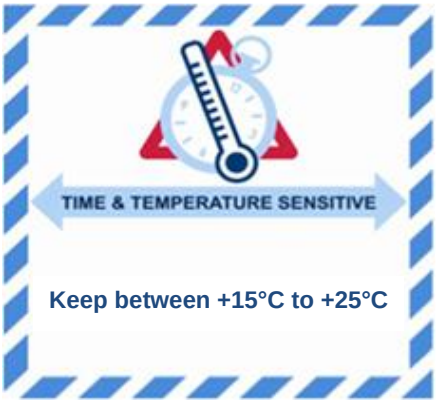
Four different business models are used for the transport of TTSPPs by air: legacy carriers; integrators; cargo only carriers, and charters. Within each category, carriers will have different service offerings and service levels tailored to the handling requirements of specific cargo.

- *Legacy carriers (Commercial airlines)*: These companies operate both passenger and cargo services and have the advantage that they service a wide range of destinations. Most of these carriers subcontract services for aircraft handling, ground handling and warehousing operations. A commercial airline's cargo business usually comes from freight forwarders and the airline involvement is limited to airport-to-airport activities. Some may offer road feeder services at origin or destination. Otherwise, a freight forwarding agent coordinates that effort.
- *Integrators:* These operate large scale door-to-door mail and express delivery services. Their product offerings are integrated under a single brand identity (i.e. FedEx, DHL and UPS). They generally deal directly with the shipper rather than a freight forwarder.
- *Cargo only carriers:* These companies do not carry passengers; they operate dedicated freighter aircraft and can carry large cargo payloads. Networks are not as extensive as the commercial airlines, which operate on a hub and spoke model. Cargo only carriers often sign contracts with large, international freight forwarders to ensure cargo space availability. Their services may include ground pick-up and delivery, so fewer stakeholders are involved. As with commercial airlines, their ground handling operations are often subcontracted.
- *Charters:* These operators allow shippers to choose between a full or partial charter. Freight forwarders with a need for dedicated space on certain high-volume trade lanes often employ charters.

2.7.2 Air transport labelling for TTSPPs

Since July 2012, the IATA Time and Temperature Sensitive label, shown in Figure 3, has been mandatory for the transport of healthcare cargo shipments. There are however, specific conditions for proper use of the label. These can be found in the current edition of the IATA Perishable Cargo Regulations, Chapter 17: *Logistics for Temperature Sensitive Healthcare Products*.

Figure 3 – Example of IATA Time and Temperature Sensitive label



Actual size 10cm x 10 cm

The principal rules for the correct use of the label are as follows:

- Shipments must be booked under the proper handling code and as temperature-controlled healthcare cargo in accordance with the IATA Perishable Cargo Regulations
- The label must be used for healthcare products only.
- The label may be applied to both active and passive shipping systems.
- The lower half of the label must indicate the external handling temperature range or limit (minimum and maximum) that the package can be exposed to during transport.
- The label is attached to a consignment which has been specifically booked as a time and temperature-sensitive healthcare product[11].
- The temperature range on the label must match the temperature range or limit stated on the AWB, SLA and/or SOP.
- The text must be in English and temperatures must be shown in degrees Celsius.
- The label must be applied by the shipper or by his designated agent.
- Only one label is required. This must be visible on the outermost means of containment (box, over-pack, or ULD).

2.8 Air transport processes

Air transport operations must be tightly managed. In addition to the tasks that must be carried out to ensure the safe arrival of a specific shipment – see Section 2.9 – there are a number of higher level precursor and recurrent actions that need to be taken. These are described below.

The shipper should:

- Conduct regular periodic training of personnel;
- Maintain an SLA with the appropriate stakeholders and transport service providers;
- Qualify the transport process to the extent possible in collaboration with the forwarder and carrier.

The freight forwarder should:

- Conduct regular periodic training for directly employed and sub-contracted personnel;
- Maintain a quality and security management system that meets the shipper's requirements;
- Maintain SLA's with subcontractors.

The air carrier and ground handlers should:

- Conduct regular periodic training of directly employed and sub-contracted personnel to ensure correct handling and transit storage of TTSPPs.

The consignee should:

[11] This is a premium service beyond that offered for general cargo.

- Conduct regular periodic training of personnel.

2.9 Managing air shipments

The actions described below apply to both active and passive shipping systems, unless specifically identified. As previously noted, some steps may be omitted or modified, but only if there is a technical justification for doing so.

Pre-shipment actions:

a. Obtain confirmation from the consignee to ship the product (e.g. purchase order or requisition).

b. Verify product dimensions and determine the type of container required.

c. Notify the freight forwarder of the shipping date and book the shipment. The freight forwarder must coordinate the transport chain and booking with the air carrier in accordance with IATA Perishable cargo regulations;

d. Communicate instructions to the freight forwarder regarding pick-up, transport and handling requirements, including transport temperature requirements.

e. Prepare shipping documentation, including checklists and air waybill (AWB) and review with the freight forwarder.

f. Arrange ground transport to airport at point or origin.

Shipping day: actions at point of origin:

a. Condition and pack the product and place activated temperature monitors within the load.

b. Label the product box to indicate the temperature range in which the shipment must be handled (see IATA PCR Chapter 17.10 for details).

c. Transport product to the freight forwarder or departure airport in a temperature controlled truck or refrigerated vehicle. The freight forwarder must obtain the shipper's approval before implementing any changes that could affect GDP or the quality of the shipped product.

Shipping day: actions at departure airport by freight forwarder:

The following action sequence assumes that the freight forwarder loads the ULD:.

a. *Active dry-ice systems only:* Load the amount of dry ice recommended by device manufacturer into the dry ice bunker. Install fresh D Cell batteries.

b. *Active systems:* Set the thermostatic controller to the desired temperature. Ensure that the container is operating properly and wait until the temperature stabilizes[12].

c. Load product into container. Ensure correct build-up of the ULD and labelling in accordance with written instructions. Do not overload. Allow for air circulation completely around product, including the bottom. Strap the load to the floor or wall stanchions to avoid shifting during transit.

d. Close door(s). Apply security seal/lock.

e. Activate and position any exterior (ambient) temperature monitors.

[12] Active ULDs are sometimes loaded at the shipper's site. A security check may then be conducted at the departure airport. This involves opening the ULD and scanning the contents.

f. Secure paperwork in the external clear-view envelope.

g. Before releasing the container to the airline, ensure that it is operating correctly and that the temperature has stabilised.

h. Transport to the airline warehouse and hand off. From this point onward the airline is responsible for maintaining the appropriate ambient temperature during storage and flight, for checking power and for re-icing the container if required, in accordance with the relevant SOP.

i. Ensure priority handling onto the aircraft.

j. Ensure all checklists are completed by responsible parties in accordance with the SOP.

k. Forward the AWB and other paperwork/instructions to the appropriate personnel.

l. Maintain tracking and traceability of the product throughout the transport process.

m. Promptly resolve and communicate any deviations.

n. Perform customs brokerage. If the ULD is opened for customs inspection the inspection made must be as short as possible and the doors must be secured again afterwards. If seals were changed, inform Shipper and/or Consignee accordingly.

<u>Shipping day: actions at by air carrier and ground handlers:</u>

a. Review the AWB and other shipping documentation with the freight forwarder and ensure that is compliant with carrier and country regulations and procedures.

b. Comply with the programmed flight schedule and ensure that adequate cargo hold space is available.

c. Communicate any delays or problems to the freight forwarder.

d. Update any temperature monitor log sheets.

e. Store the product in conditions that are within the defined temperature range on the label and AWB.

f. Minimize the elapsed time between warehouse and aircraft loading/unloading (tarmac time).

g. Handle active and passive shipping systems in accordance with shipper's instructions.

h. Load the consignment in the aircraft. Wherever possible, avoid placing temperature-sensitive freight near the aircraft cargo door.

i. Maintain recommended cargo hold temperature settings.

j. Transport the product from the departure airport to the destination airport.

k. Store the product at transit airports in an area kept within the specified handling temperature range.

l. Inform the freight forwarder of arrival.

<u>Arrival day: actions at destination:</u>

a. Ensure priority unloading from the aircraft.

b. Handle active and passive shipping systems in accordance with shipper's instructions.

c. Store the product at the arrival airport in an area kept within the specified handling temperature range.

d. *Active systems:* Check that container is operating properly. Re-ice and replace batteries if required.

e. *Active systems:* Record the temperature as shown on the outside display panel.

f. Freight forwarder assists with customs clearance and logs receipt of the product from the service provider.

g. Provide clear instructions for either unloading the container at the airport or for transporting to the consignee.

h. Inspect goods for physical damage and evidence of temperature abuse.

i. Ensure all checklists are completed by responsible parties.

j. Consignee receives product, retrieves and deactivates EDLMs for data retrieval, if applicable.

Post shipment actions:

a. Forward completed checklists to appropriate personnel, including the electronic temperature data files.

b. Transport the empty container to the ground handler, check for damage and functionality.

c. Return any packaging and/or temperature monitoring devices, if applicable.

d. Forwarder collects all pertinent data, checklists, etc., to complete shipment.

A similar international shipping procedure has been developed by UNICEF Supply Division specifically for shipping vaccines in passive containers. This process, together with the UNICEF Vaccine Arrival Report form, is described in EVM-SOP-E1-02: *Vaccine arrival procedures.*

References

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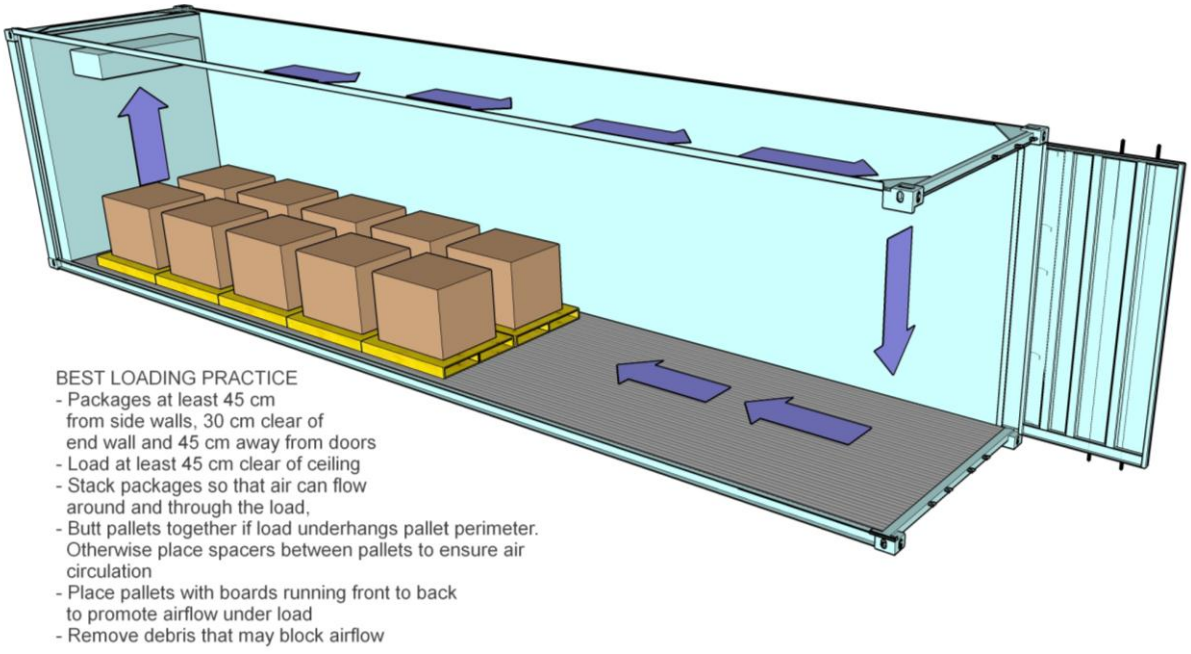
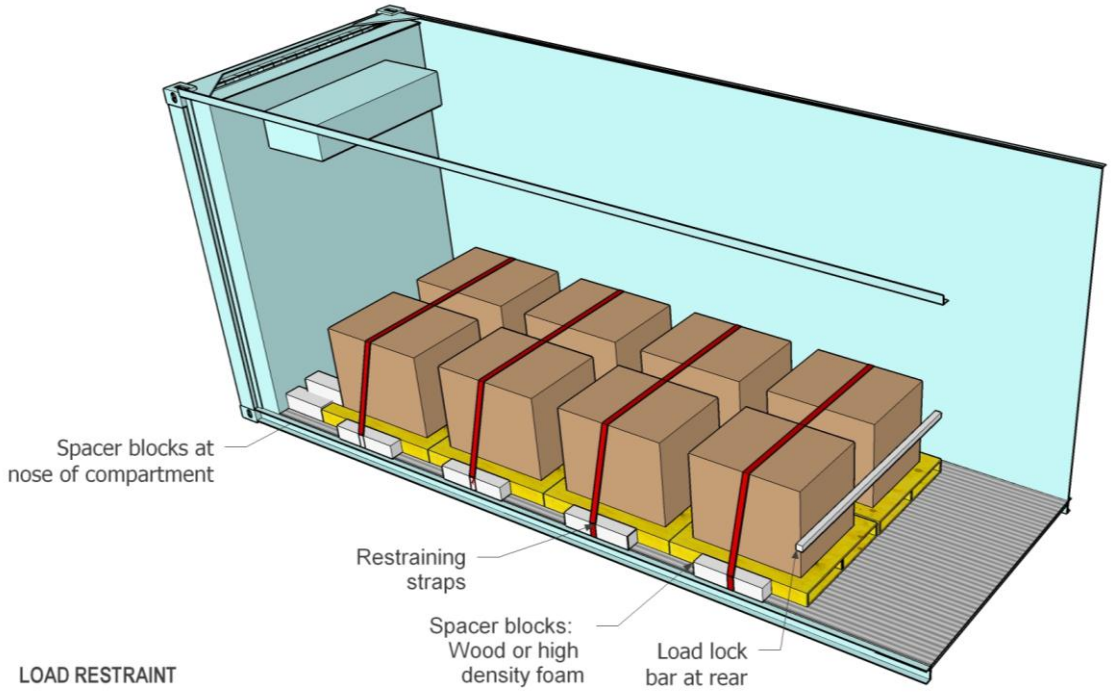
Annex 1 – Packing a refrigerated vehicle

The following diagrams show the correct procedure for packing pallets in a refrigerated vehicle.





Revision history

Date	Change summary	Reason for change	Approved