GUIDELINES ON THE INTERNATIONAL PACKAGING AND SHIPPING OF VACCINES, SIXTH EDITION

World Health Organization

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CONTENTS

ABBREVIATIONS

°C	degree Celsius
°F	degree Fahrenheit
AWB	airway bill
BCG	bacille Calmette–Guérin (tuberculosis vaccine)
CCM	cold chain monitor (card)
cm^3	cubic centimetres
cPAD	compact pre-filled auto-disable (system)
DT	diphtheria-tetanus (vaccine)
DTP	diphtheria-tetanus pertussis (vaccine)
DTP-HepB-Hib	diphtheria-tetanus -pertussis, hepatitis B, *Haemophilus influenzae* type B (vaccine)
EPROM	erasable programmable read-only memory
ETA	estimated time of arrival
HepB	hepatitis B (vaccine)
Hib	*Haemophilus influenzae* type B (vaccine)
HPV	human papillomavirus vaccine
IPV	inactivated polio vaccine
IATA	International Air Transportation Association
JE	Japanese encephalitis (vaccine)
kg	kilogram
L	length
LCD	liquid crystal display
LED	light-emitting diode
LRC	lot release certificate
LSP	logistics service provider
MKT	mean kinetic temperature
MMR	mumps-measles-rubella (vaccine)
MR	measles-rubella (vaccine)
MVP	(Division of) Medicines, Vaccines and Pharmaceuticals (WHO)

NRA	national regulatory authority
OCV	oral cholera vaccine
OPV	oral polio vaccine
OQ	operational qualification
PAHO	Pan American Health Organization
PCV	pneumococcal conjugate vaccine
PDF	portable document format
PQ	performance qualification
PQS	Performance, Quality and Safety (WHO)
PQT	Pre-Qualification Team (WHO)
RV	rotavirus vaccine
SD	Supply Division (UNICEF)
SLP	summary lot protocol
Td	tetanus toxoid and diphtheria (reduced component) vaccine
TT	tetanus toxoid (vaccine)
TTI	time and temperature integrator
UN	United Nations
UNICEF	United Nations Children's Fund
USB	universal serial bus
VAR	vaccine arrival report
VPPAG	Vaccine Presentation and Packaging Advisory Group
VVM	vaccine vial monitor
W	width
WHO	World Health Organization
YF	yellow fever (vaccine)

GLOSSARY

Ambient temperature

The prevailing temperature within a defined environment or series of environments, such as a supply chain.

Bar code

A label containing symbols that can be scanned electronically using laseror camera-based systems. Barcodes are used to encode information such as product numbers, serial numbers and batch numbers. Barcodes can facilitate automated data capture to improve vaccine distribution and inventory management.

Blow-fill-seal (BFS) container

Plastic containers that are extruded, blown, filled and sealed in a single, continual process. BFS is an aseptic filling process that is widely used in the pharmaceutical industry. BFS containers can be produced in large volumes at a low cost.

Cold spot

A cold spot refers to the lowest temperature value(s) recorded in the space over the study period, but with these lowest temperature value(s) remaining within the specified temperature range (e.g. cold spots identified between +15°C to +17.5°C in a room with a specified temperature range +15°C to +25°C).

Dunnage

Loose packing material (packaging peanuts, air cushions, bubble wrap, plastic air bags, paper) used to protect contents of shipping containers from damage during transport. It also helps to prevent contents from shifting during transport by filling voids.

Q-tag® CLm doc from Berlinger & Co. AG – PQS code E006/016

LogTag® TIC20 from LogTag Recorders – PQS code E006/021

VaxAlert™ from Sensitech PQS code E006/010

Endicate® from Switrace SA PQS code E006/063

Electronic data integrator (EDI)

A hybrid electronic with the report/data-producing capabilities of an electronic data logging monitor (EDLM). An EDI combines the features and functions of a go/no-go device (like an indicator) with the record retention and data tracking facility of an EDLM, but with greater granularity and data management flexibility. It uses preprogrammed temperature threshold intelligence to integrate post-analytic functional steps that are typically performed by trained personnel.

Examples of WHO PQS prequalified electronic data integrators

TempTale® Ultra from Sensitech Inc. PQS code E006/046

Libero Ti1 from Elpro-Buchs AG PQS code E006/024

LogTag® TRIX-8 from LogTag Recorders PQS code E006/006

Examples of WHO PQS prequalified electronic data logging monitors

Electronic data logging monitor (EDLM)

A compact, portable device that measures, temperature over time by means of a built-in sensor. EDMLs 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 a power source (coin cell).

Erasable, programmable read-only memory (EPROM)

A type of programmable read-only memory chip that retains its data when its power supply is switched off.

EURO pallet

The standard European pallet, as specified by the European Pallet Association (EPAL). The EUR pallet is 1200x800x144 mm; it is a four-way pallet made of wood that is nailed with 78 special nails in a prescribed pattern. *(Pharmaceutical and Vaccine Quality Illustrated).*

Freight forwarder

A person or company who undertakes to handle the movement of goods from point to point on behalf of the cargo owner.

Grouping case

The package presentation containing multiple secondary packages.

GS1

A neutral not-for-profit international organization that facilitates the development and maintenance of standards for supply and demand chains across multiple sectors. The GS1 General Specifications system is designed to standardize supply chain data to identify, capture and share uniform, accurate data.
It includes standards that define unique identification codes that may be used by an information system to refer to a real-world entity, such as a logistics unit. Use of GS1 standards for barcodes facilitates the international supply chain management of vaccines.

Hot spot

A hot spot refers to the highest temperature value(s) recorded in the studied area over the study period, but with these highest temperature value(s) remaining within the specified temperature range (e.g. hot spots identified between +7°C to +8°C in a cold room with a specified temperature range +2°C to +8°C).

House airway bill (HAWB)

Issued by a freight forwarder (consolidator) to a shipper as a receipt for the goods which will be shipped with other cargo as one consignment to avail of better freight rates. The airline's (carrier's) AWB shows the forwarder as the consignor and the name of forwarder's agent at the destination as the consignee. Although it is not a complete document of title, a forwarder's AWB has a legalstanding similar to that of a carrier's AWB. Also called forwarder's air waybill. *(Business Dictionary).*

Index shipping box

The shipping box containing international shipping documents.

Insulated shipping container

A single-use, insulated, passive container that holds coolant-packs, typically used for the international shipment of vaccines from the manufacturer. Insulated shipping containers help keep vaccines at appropriately cool temperatures during shipment. However, they can be a challenge for countries to dispose of after use.

Logistics service provider (LSP)

A company that provides management over the flow of goods and materials between points of origin to end-use destination. The provider usually handles shipping, inventory, warehousing, packaging and security functions depending on the service level agreement signed between involved parties.

Operational qualification (OQ)

The process of obtaining and documenting evidence, under controlled conditions, that the premises, equipment and supporting systems operate in accordance with their design specifications.

Package insert

A document containing detailed information about a vaccine (for example, clinical pharmacology, indications for use, contraindications). It is generally placed inside the vaccine product's secondary packaging. Any change to a vaccine must be reflected in its package insert. Package inserts are a regulatory requirement for vaccines and provide instructions to healthcare providers on vaccine use and other key product information.

Pallet

Wooden or plastic platform designed to be lifted by pallet jack or forklift truck. Typically used for storing and handling tertiary cartons.

Since pallets form an important part in the maritime industry, several norms and measures have been established by the ISO (International Organization for Standardization). Use of such norms aims to bring the entirety of the freight operations which palletize their cargo consignments under a wider and common spectrum. The normative standardization for pallets has been regulated in their sizing. Pallet sizes matter hugely while loading on palletized cargo ships as depending on the nature of the cargo, the optimal sized pallet is utilized to support the cargo consignments. *(Pharmaceutical and Vaccine Quality Illustrated).*

Pallet shipper

A combination of different products stacked together and wrapped on a pallet for shipment to a retailer. It provides bulk holding of pharmaceutical products either in single or multiple payload cavities with the advantage of increasing the payload and thus reducing shipping cost. *(Pharmaceutical and Vaccine Quality Illustrated).*

Performance qualification (PQ)

The process of obtaining and documenting evidence that the premises, equipment and supporting systems, as connected together, will consistently perform in accordance with the approved process method and specifications.

Prequalified

Describes a product that has successfully completed the WHO prequalification process, which aims to ensure that vaccines and immunization-related devices for high-burden diseases meet global standards of quality, safety, efficacy and programmatic suitability in order to optimize use of health resources and improve health outcomes. Vaccines and devices that have been WHOprequalified meet global standards for quality and appropriateness. They can be procured by United Nations agencies.

Primary container

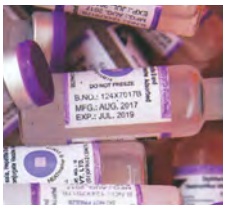
A first level package presentation that is in direct contact with the product itself. Main purpose of the primary pack is to protect, preserve and contain the product. Delivery devices that are combined with vaccines or contain vaccines are considered primary containers. Vaccine primary pack (container) comes in various types, e.g. vial, ampoule, tube, microarray patch, compact prefilled auto-disable (cPAD system), blow-fill-seal (BFS) container, pouch, sachet or bottle.

Secondary pack or carton

The package presentation intended for the end-user (e.g. bottle + cap liner + dose cap + leaflets + carton) but not including packaging used solely for transport purposes (e.g. Tertiary carton or Insulated shipper). The secondary pack may contain multiple units of product.

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 minimumlevel performance, operation or other service attributes. SLA is also known as “quality agreement” and “technical agreement”.



Shelf life

The period of time during which a product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch. Shelf-life is used for the final product; storage period is used for intermediate products.

Stability budget

A stability budget considers long term, accelerated, and stress temperature exposure, as well as temperature cycling studies to determine the amount of time out of storage that a drug product may experience without any significant risk to its quality (*PDA*). Temperature sensitive products may have limited time that they can be exposed to temperature outside label storage conditions and still meet quality attributes through expiry. The stability budget ensures product will meet shelf life specifications given end to end time out of storage requirements.

Tertiary pack or carton

The pack or carton that contains a number of secondary cartons or grouping cases; usually constructed of corrugated fibreboard. The tertiary carton is not the same as the insulated shipper used for international air shipment of time- and temperature-sensitive pharmaceutical products, although the insulated shipper may contain one or more of these cartons.

Vaccine vial monitor (VVM)

A label containing a heat-sensitive material which is placed on a vaccine vial to register cumulative heat exposure over time. The combined effects of time and temperature cause the inner square of the vaccine vial monitor to darken gradually and irreversibly. A direct relationship exists between the rate of colour change and temperature: the lower the temperature, the slower the colour change; the higher the temperature, the faster the colour change. VVM is the only type of temperature indicator that is available at any stage in the process of distribution and at the stage that a vaccine is administered, indicating whether the vaccine has been exposed to a combination of excessive temperature over time and whether it is likely to have been damaged.

PREFACE

The *Guidelines on the international packaging and shipping of vaccines* document has been one of the most widely-used manuals in the field of immunization. It is referenced by UNICEF and PAHO in all their invitations to bid for vaccine supplies and also by countries that directly procure their vaccines.

This 2020 edition brings considerable changes to the previous ones. All changes are listed in Revision History on page 164.

WHO recommends that all United Nations (UN) procurement agencies include the *Guidelines on the international packaging and shipping of vaccines* as part of the technical specifications and requirements in invitations to bid.

This document has been reviewed through two public consultations in 2019 and 2020. WHO thanks all individuals, organizations, national regulatory authorities and industry members for their contribution.

INTRODUCTION

International shipping of vaccines is the first leg of the complex journey that vaccines undertake to reach the end users in a country. Particular challenges include the size and weight of packages, implementation of quality control checks at reception, ensuring environmental sustainability, and maintaining required temperatures during the journey. Although there are many possibilities of transport e.g. sea freight and terrestrial transportation, air freight currently remains the most widely used means of transport for vaccines. In recognition of this fact, these *guidelines* apply predominantly to the air freighting of vaccines. Transportation of vaccines from the manufacturing facility to the airport facility require the use of ground transportation, and reference is also made to the qualification of refrigerated road vehicles as well.

The objective of these *guidelines* is to provide technical guidance to help ensure the quality of vaccines during all stages of the international air transportation process. These *guidelines* are applicable to all persons and institutions involved in international air shipment of vaccines from the premises of the product manufacturer to the recipient country. This includes all parties involved in shipment, vaccine manufacturers, logistics service providers (LSPs), freight forwarders, carriers and their employees. The relevant sections of these *guidelines* should also be considered for implementation by UN procurement agencies and other international procurement organizations, countries, donor agencies and certifying bodies.

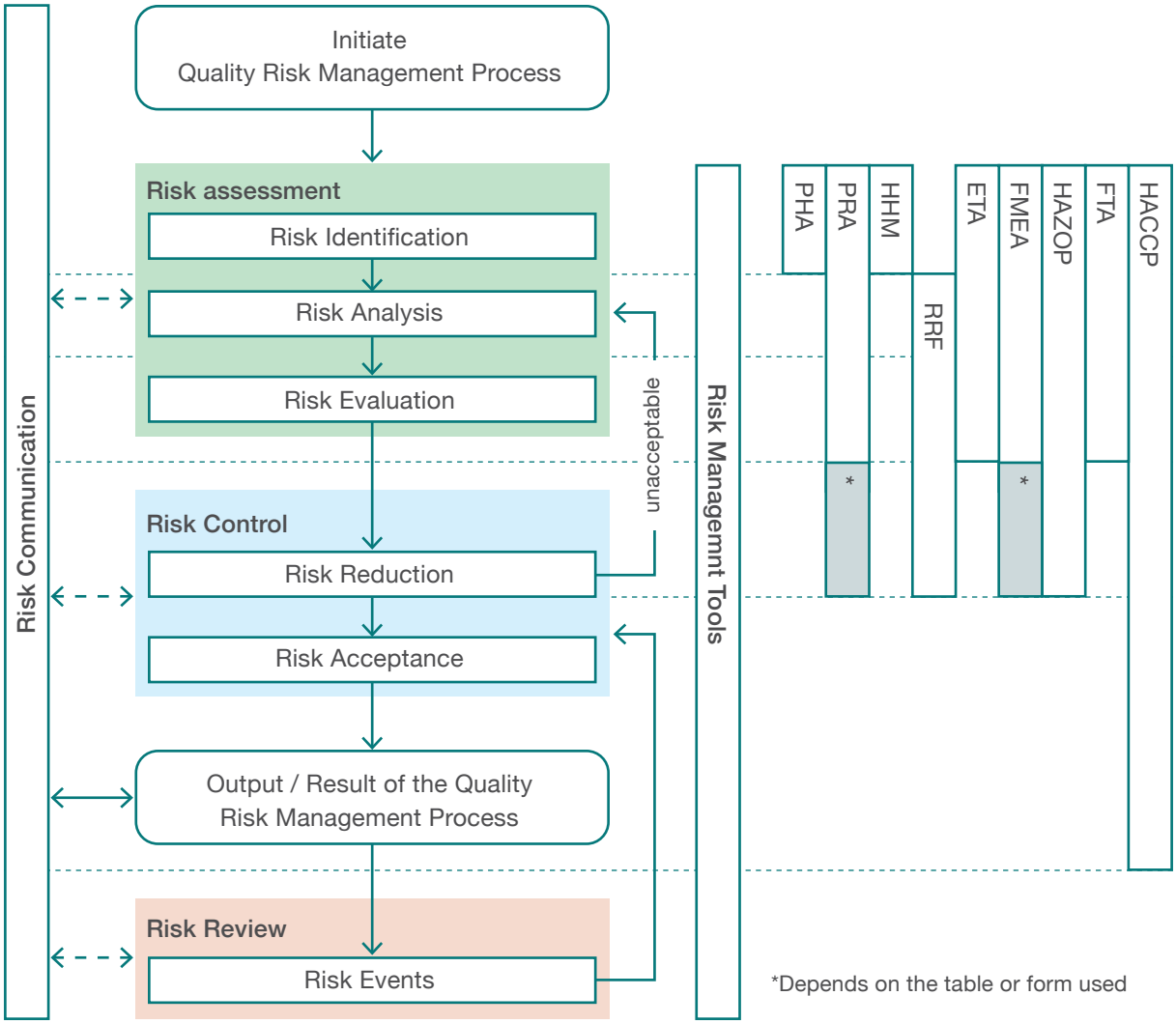
In order to maintain the original quality of vaccines, every party actively involved in international air shipment has to comply with these *guidelines*. They are referred to as contractual obligations by international procurement agencies.

Vaccine manufacturers and contracted parties such as LSPs and freight forwarders, as well as responsible official bodies of recipient countries, are expected to conduct risk assessments to assess potential risks to the quality and integrity of vaccines during the air freight and receipt operations. A quality system should be in place and should be implemented to address any potential risks that are identified. The quality system should be reviewed and revised periodically to address new risks identified during a risk assessment.

Several informal and formal risk assessment tools can be used to conduct risk assessments and control risks.

Figure 1 illustrates the risk management process and tools to use.

Figure 1. Risk management process and tools to use (J. Vesper).



Legend

- PHA (preliminary hazard analysis);
- PRA (preliminary risk analysis);
- HHM (hierarchical holographic modelling);
- RRF (risk ranking and filtering);
- ETA (event tree analysis);
- FMEA (failure mode and effects analysis);
- HAZOP (hazard and operability studies);
- FTA (fault tree analysis);
- HACCP (hazard analysis and critical control point).

2. INSULATED PACKAGING STANDARDS

2.1 Introduction

In order to protect the vaccines from exposure to both extreme temperatures and physical damage during international air transportation, WHO requires manufacturers to pack and ship vaccines in insulated shipping containers. The vaccine should be kept at recommended temperature range during transport with the help of coolants packed inside the shipping containers.

In addition to the thermal insulation, shipping containers must be designed to ensure they withstand the physical conditions encountered during international transportation by air.

2.2 Classification of vaccines for packaging

Vaccines are classified into three categories for their packaging for international air shipments on the basis of their thermostability and presentation (see Table 1).

Table 1. Classification of WHO prequalified vaccines based on their thermostability and presentations for international air shipment.

Class A – Highly heat sensitive and not impacted by freezing	Recommended Shipping Temperatures	
	Lower Limit	Upper Limit
Oral polio vaccine bivalent types 1 and 3 Oral polio vaccine monovalent type 1 Oral polio vaccine type 2 Oral polio vaccine type 3 Oral polio vaccine trivalent	None	8 °C
Class B – Heat sensitive and not impacted by freezing	**Recommended Shipping Temperatures**	
	Lower Limit	**Upper Limit**
bacille Calmette–Guérin Haemophilus influenzae type b (lyophilized) Influenza, pandemic H1N1 (lyophilized) Influenza, seasonal (lyophilized) Japanese Encephalitis vaccine (live, attenuated - lyophilized) Measles Measles-Rubella Measles-Mumps-Rubella Meningococcal A conjugate Meningococcal ACYW-135 (conjugate vaccine - lyophilized) Rabies vaccine (inactivated - lyophilized) Rotavirus (live attenuated - lyophilized) Rotavirus (live attenuated – liquid, applies only to products from Bharat) Rubella (live attenuated – lyophilized) Varicella Yellow fever	None	8 °C

Class C – Heat sensitive and impacted by freezing	Recommended Shipping Temperatures	
	Lower Limit	Upper Limit
Diphtheria-Tetanus Tetanus-Diphtheria (reduced content) Diphtheria-Tetanus-Pertussis (acellular) Diphtheria-Tetanus-Pertussis (acellular)-Hepatitis B-Haemophilus influenzae type b-Polio (inactivated) Diphtheria-Tetanus-Pertussis (whole cell) Diphtheria-Tetanus-Pertussis (whole cell)–Haemophilus influenzae type b Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenzae type b Haemophilus influenzae type b (liquid) Hepatitis A (inactivated) Hepatitis B Human papillomavirus (quadrivalent, bivalent and nine-valent) Influenza, pandemic H1N1 (liquid) Influenza, seasonal (liquid) Japanese Encephalitis vaccine (inactivated) (liquid) Meningococcal ACYW-135 (conjugate vaccine) (liquid) Oral cholera vaccine Pneumococcal (conjugate) Polio vaccine (inactivated) Rotavirus (live attenuated) (liquid) Tetanus toxoid Typhoid (polysaccharide and conjugate)	2 °C	8 °C

WHO now offers an updated spreadsheet with all WHO prequalified vaccines and their packaging class. This spreadsheet can be downloaded from link: https://tinyurl.com/y2wopnrb.

2.3 Use of coolants in international air shipments

WHO recommends use of water-based packs (frozen or chilled depending on the class of packaging) or packs with phase change materials (PCM). All vaccine manufacturers are encouraged to qualify their class A and class B packaging with frozen packs or appropriate phase change materials in order to phase out the use of solid carbon dioxide or dry ice. Shipments containing dry ice pose several risks during transit, including a risk of explosion, suffocation and tissue damage. In addition, there are limitations to the loading amount of dry ice depending on the aircraft capacity, which may result in split shipments. Due to its hazardous nature, dry ice is therefore regulated as a “dangerous good” by the International Air Transport Authority (IATA).

A water-based coolant pack

In order to mitigate these risks several precautions must be taken when offering packages containing dry ice for shipment:

1. **Gas venting**: Dry ice must never be sealed in a container with an airtight seal such as a jar with a threaded lid or a plastic cooler. Dry ice should be packed loosely in the outer package such as expanded polystyrene (EPS). Packages must allow for the release of carbon dioxide gas.
2. **Package integrity**: A package containing dry ice must be of adequate strength for intended use. It must be strong enough to withstand the loading and unloading normally encountered in transport. It must also be constructed and closed in order to prevent any loss of contents that might be caused by vibration or by changes in temperature, humidity or altitude.
3. **Package materials**: Plastics that can be rendered brittle or permeable by the temperature of dry ice should not be used. This problem can be avoided by using commerciallyavailable packages intended to contain dry ice.
4. **Air Waybill (AWB)**: The AWB must include the statement “Dry ice, 9, UN1845, number of packages <X> net weight in kilograms <Xkgs>.”
5. **Labeling**: The outermost container must be labeled on two opposing sides of the box with a hazard class 9 label, UN 1845 and net weight of dry ice in kilograms.

Most coolant packs can be reused. However, if they are non-standard size compared to ones used for in-country distribution, they present a challenge for configuring the positioning and number of packs to be used with common cold boxes and vaccine carriers at the country level. If not reused all packs require disposal, which may have an environmental impact and may add cost. Returning them to manufacturer is considered to be uneconomical.

Whilst most of the PCMs used by the industry are non-toxic to humans and animals, ingestion and long-term exposure to skin should be avoided. In regards to disposal, PCM materials are land-fillable (subject to federal, state and local regulations) and are not considered a hazardous waste or hazardous material. However, given their high energy content, incineration is preferred over landfill disposal.

2.4 Diluents in international air shipments

Diluents for lyophilized vaccines must always be included with the vaccine shipment in a quantity that matches the quantity of vaccine; diluents however do not require temperature-controlled packaging unless specifically requested by the manufacturer. However, it should be noted that two different temperature regimes cannot be marked for the shipment that is on the same airway bill (AWB) according to IATA rules. If freezing temperatures are requested to be maintained throughout the air shipment, the manufacturer must submit supportive data to demonstrate that freezing has no impact on the diluent and no impact on the physical integrity of the ampoule/vial/tube as it relates to the quality, safety and potency of the vaccine. The same requirement is in place for the lyophilized vaccines that are bundled in one secondary package with their diluents. In the absence of such supporting data, for lyophilized vaccines bundled in the same packaging with their diluents, Class C packaging would apply.

2.5 General packaging criteria

Shipping containers are defined as an outer, insulated box designed to package and transport vaccines during international shipment by air. This can either be an individual insulated shipping carton or a pallet shipper.

Shipping containers must be of sufficient durability to protect vaccines against mechanical manipulation, repeated manual handling and environmental conditions whilst keeping the physical integrity and properties intact and ensuring carton quality is maintained throughout the shipment. Design of the shipping containers can be guided by tests proposed in ASTM D4169 *Standard Practices for Performance Testing of Shipping Containers and Systems* or *ISTA 3 Series General Simulation Performance Test Procedure*. WHO requires manufacturers to qualify their shipping containers in refer to Technical Supplement 13 – *Qualification of shipping containers,* and *Technical Supplement* 14 – *Transport route profiling qualification* (Technical supplements to WHO Technical Report Series, No. 961, 2011 – Annex 9: Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products).

Coolant packs or PCMs placed inside shipping containers must be of satisfactory durability to ensure they do not leak or crack during repetitive or poor handling.

2.6 Weight and size of insulated shipping cartons

Although mechanical equipment is used in shipping operations, manual handling is common during assembling the load at manufacturing facility and offloading the shipping containers for storage at the recipient end. The manual handling of a load may present a risk particularly of back injury if it is too heavy or too large, unwieldy or difficult to grasp, and unstable or has contents likely to shift.

Insulated containers (cartons) used for shipping vaccines should not weigh more than 50 kg each at full weight.

It is the employers' responsibility to carry out manual handling risk assessment to assess any manual handling or lifting that an employee is required to do as part of their work. Manual handling risk assessments should be part of the organizational culture of vaccine manufacturers and Ministries of Health in the recipient countries.

Vaccine manufacturers are advised to pack shipping containers in such a way that the contents of the container will not shift during handling. When necessary, any voids in the container should be filled with dunnage. Dry ice will reduce in volume as it depletes, and dry ice must be contained in its own carton for shipments to avoid empty space within packaging and the risk of product shifting.

In addition, insulated cartons should be of suitable dimensions to enable efficient stacking on ISO pallets without overhanging the pallet footprint. Pallets come in different sizes.

Table 2. Flat pallets for intercontinental materials handling – principal dimensions and tolerances (ISO 6780).

Dimensions (WxL) in millimeters	Dimensions (WxL) in inches	Unused floor space in 40' ISO container	Region
1016x1219	40x48	3.7%	North America
1067x1067	42x42	11.5%	North America, Europe, Asia
1000x1200	39.37x47.24	6.7%	Europe, Asia
800x1200	31.5x47.24	15.2%	Europe (fits many doorways)
1165x1165	45.9x45.9	8.1%	Australia
1100x1100	43.3x43.3	14%	Asia

2.7 Insulated pallet shippers

Insulated pallet shippers provide bulk holding of products either in single or multiple payload cavities. They also confer the advantage of increasing the payload and thus reducing shipping cost.

Pallet shippers have a built-in wooden or plastic pallet platform to enable handling and transport by forklift or pallet handling equipment. Pallet shippers will generally accommodate higher volumes of vaccines per unit, normally with a lower ratio of coolants to vials compared to the same volume of insulated shipping cartons.

It is recommended that the external dimensions of pallet shippers for vaccines procured through UNICEF, PAHO or other UN procurement agencies should not exceed standard ISO pallet sizes. The height of pallet shipper should not exceed 1600mm.

Where manufacturers wish to introduce the use of pallet shippers for international air shipments of vaccines, the UN procuring agencies must be consulted. Based on the capacity of the receiving country as well as the capacity of the airline, the procurement agency may agree to a transition plan with respective countries prior to introduction.
Due to infrastructure and logistics constraints in some receiving countries, manufacturers must ensure smaller pallet shippers.

Figure 3. Polyisocyanurate made different size insulated pallet shippers with one and two cavities.

2.8 Cargo covers (pallet covers, pallet blankets, thermal blankets)

Pallet covers, pallet blankets and thermal blankets are terms that are used interchangeably to describe a range of flexible cover systems which are fitted over entire pallets of temperature sensitive goods. Cargo covers are designed to provide protection during short breaks in the cold chain, such as during loading and unloading at airports and other cross-docking operations. Cargo covers use combinations of flexible insulation and metallic, radiant barrier materials to enhance the overall level of insulation of a packaging system. Some cargo covers also have a white, highly reflective outer surface which additionally reduces heat-load during outdoor exposure to solar radiation.

In the shipment of vaccines, cargo covers may be used as an additional risk mitigation approach, applied over the insulated shipping cartons or pallet shippers described above.

Cargo covers are typically available in a range of sizes designed fit over ISO standard pallets in varying load heights. Thicker covers (some can be up to 10 cm) may increase the external dimensions of the load beyond the standard pallet size.

The use of stretch wrap or other plastic films applied over cargo covers should be avoided where possible; it can create greenhouse effect if exposed to strong sunlight which can significantly reduce the effectiveness of the insulation materials below. This applies also to insulated shipping boxes and pallet shippers. A well-designed cargo cover should provide sufficient protection from rain, snow, dust, pests and other contamination, making stretch-wraps or films unnecessary.

Figure 4. Examples of cargo covers.

Laminated double metallized bubble-wrap cover

Laminated multi-layer metallized thermal blanket

Tyvek®XtremeTM W50 cargo cover

2.9 Active vs. passive air shipment systems

A typical active air shipping system is a dedicated portable container, which may be one of two types: systems with cooling only and systems with both heating and cooling. Temperature control is ensured via a temperature-stabilizing medium which is either dry ice in the case of cooling active systems, or phase change materials in the case of heating and cooling active systems. Alternatively, compressor-driven cooling systems are also widely used. These containers are either powered by onboard batteries or by an external electrical source to run onboard 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, from an air or ocean carrier, or from a third-party logistics service provider.

Although stable temperatures can be maintained for prolonged periods, active packaging systems with a mechanical refrigeration are not to be used for the international shipment of vaccines unless specifically requested by the procuring UN agency. This is because of other limitations of these systems, such as requiring constant power supply and batteries to be periodically recharged, their need for power/fuel/ice availability which imposes tight restrictions on handling and shipping, and their requirement for serviced destinations.

WHO recommends use of passive container systems for international air transport of vaccines, unless use of an active system is specifically requested by the UN procuring agency. Passive systems maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of preconditioned coolant in the form of chilled or frozen packs, phase change materials, dry ice or others.

3. TRANSPORT ROUTE PROFILING AND QUALIFICATION OF SHIPPING CONTAINERS

WHO no longer requires stress testing for qualification of shipping containers. All vaccine manufacturers are now required to use transport route profiling data, either from actual historical shipments or experimentally generated using dummy shipments, and degree-hour calculations to derive a test profile. Manufacturers must then apply this as a basis for conducting operational qualification (OQ) of packaging solutions under laboratory conditions in a temperature-controlled test chamber (using the test profile derived from degree-hour calculations).

3.1 Transport route profiling qualification

Regulators increasingly require pharmaceutical transport operators to document their shipping practices in a manner which shows that they fully understand their transport process and are able to maintain control over it. As part of the process of validating these practices, the operational qualification (OQ) and performance qualification (PQ) of shipping containers and refrigerated vehicles should be based on a transport route profile(s) which reflects the real distribution environment in a statistically robust manner. Consequently, the initial route profiling exercise should be carried out before actual products are distributed. Historical route profile data used for the shipment of other vaccines can be used to qualify packaging for new vaccines.

The fundamental purpose of a transport route profiling study is to collect temperature data that accurately represent real distribution practice. Once a representative ambient profile has been derived it can be used to qualify a shipping system whose performance aligns with the specific operational context. Supplement 14, *Transport route profiling qualification* (Technical supplement to WHO Technical Report Series, No. 961, 2011 – Annex 9: Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products) sets out the data collection and data analysis process and describes a simple approach for matching a shipping system with a profile – the *degree-hour* method. All manufacturers should refer to this supplement in establishing transport route profiles. Target temperature range should be the recommended transport temperatures as indicated on the label. The supplement is reprinted in full in *Annex 1*.


ANNEX 1.

SUPPLEMENT 14

TRANSPORT ROUTE PROFILING QUALIFICATION

TECHNICAL SUPPLEMENT TO WHO TECHNICAL REPORT SERIES, NO. 961, 2011

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

3.2 Qualification of shipping containers

Transport operators and end-users need to be confident that vaccines will be delivered in container systems that are capable of maintaining a predefined internal temperature range during transport, that can minimize product degradation as a result of temperature-sensitivity, and that can meet the product stability profile requirements stated by the pharmaceutical manufacturer. Regulatory authorities and other interested parties require documented evidence that compliance with these requirements can be demonstrated and maintained.

Every shipping container system must be fully qualified to show that it is "fit for purpose" and capable of maintaining a vaccine within the temperature range needed to meet the product manufacturer's stability profile, under the anticipated transport conditions. As indicated in the *"Supplement 14, Transport route profiling qualification"*, *Method A* (operational qualification) should be used to qualify shipping containers. *Method A* uses the collected route profile data to create a statistically robust test profile; this can then be used as a basis for testing proposed packaging solutions under laboratory conditions in a temperature-controlled test chamber. WHO does not recommend use of *Method B* for qualification of international shipping containers since real life temperatures may fluctuate above and below 0.0°C. *Method B* is an empirical rule-of-thumb approach, for use where the performance of the proposed passive container is already known, because it is based on a simple empirical calculation, it is strongly recommended that this method should only be used for in-country transport operations.

Qualification must also demonstrate that the system can sustain handling and transport while protecting the physical integrity of the product. Manufacturers should refer to Supplement 13, *Qualification of shipping containers* (Technical supplement to WHO Technical Report Series, No. 961, 2011 – Annex 9: Model guidance for the storage and transport of timeand temperature-sensitive pharmaceutical products) for OQ and PQ of shipping containers. Although the main focus of this document is the PQ, manufacturers are requested to conduct OQ of shipping containers using the transport route profiles created based on degree-hour method. The document is also fully reproduced in *Annex 2*.


ANNEX 2.

SUPPLEMENT 13

QUALIFICATION OF SHIPPING CONTAINERS

TECHNICAL SUPPLEMENT TO WHO TECHNICAL REPORT SERIES, NO. 961, 2011

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The PQ stage is mandatory in all cases, except where every shipment on every route is monitored. PQ is conducted as a field test in the real operating environment. A PQ protocol must be developed to document the process and define the acceptance criteria; these criteria should be similar to those defined in the OQ protocol.

The PQ protocol should be representative of existing shipping operations and must include the:

- number of “ship-to” locations,
- number of “ship-from” locations,
- number of shipments to be tested, and
- time of year the shipments are to occur.

As with the OQ, PQ tests must be performed three times, and they must successfully meet the acceptance criteria in every instance in order to demonstrate repeatable performance. Once the PQ is complete, a final report which documents the test results and compares them with the PQ acceptance criteria must be prepared.

In the case of using pallet shippers, transport route profiling qualification, OQ and PQ also apply.

Manufacturers are requested to file the following reports in support of qualification of their shipping containers:

- transport route profiling study results,
- operational qualification (OQ) of the shipping container, and
- performance qualification of the shipping container.

Although during the OQ and PQ, target temperature range is the product transport temperature as recommended by the manufacturer (and indicated on the label), the temperature monitoring devices recommended by WHO have alarms based on stability budgets of the products. These alarm settings cannot be used as target temperatures for OQ and PQ of the shipping containers.

Note on decimal rounding: during storage and distribution of vaccines, in different temperature scales with 0, 1 or 2 decimal places, it is recommended to apply rounding rules to evaluate reported temperature data expressed in whole numbers, to be aligned with controlled cold temperature limits reported without decimals as mentioned in international pharmacopeias and guidelines.

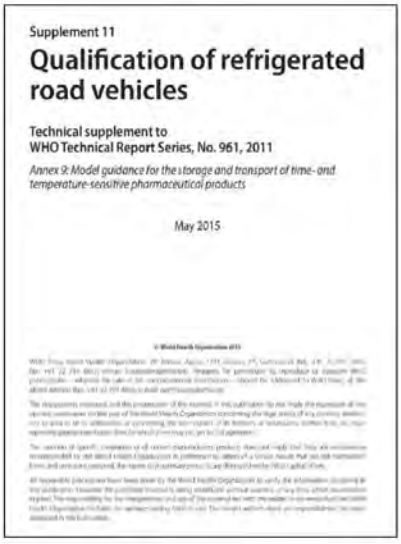
When rounding is required, consider only one digit in the decimal place to the right of the decimal place to which the numeral is to be rounded. If this digit is smaller than 5, it is eliminated and the preceding digit is unchanged. If this digit is equal to or greater than 5, it is eliminated and the preceding digit is increased by 1”. In any case, numbers should not be rounded until the final calculations for reportable value.

3.3 Qualification of refrigerated road vehicles

Where refrigerated vehicles are directly owned and/or operated it is important, wherever possible, to qualify each vehicle before it becomes operational. In addition, where a contract carrier service is used, the shipper has a duty to ensure that the carrier's vehicles are appropriately qualified.

The qualification procedure should:

- **Demonstrate** that the temperature distribution within the pay load area of the temperature-controlled compartment is maintained within the range specified for the products being transported (e.g. +2.0°C to +8.0°C). The qualification procedure must be able to assess actual product temperatures for commonly used load layouts. Qualification should be carried out at the ambient temperature extremes anticipated during normal operation, over known distribution routes.
- **Define** zones within the vehicle's payload area that 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 or minimum in the event that the temperature- controlling unit fails. Similar tests should be used to validate the anticipated door-opening times that will occur during deliveries.
- **Document** the qualification exercise for internal quality assurance and external regulatory purposes.


Supplement 11

Qualification of refrigerated road vehicles

Technical supplement to
WHO Technical Report Series, No. 961, 2011

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

May 2015

For details of the qualification of refrigerated road vehicles, refer to Supplement 11, *Qualification of refrigerated road vehicles* (Technical supplement to WHO Technical Report Series, No. 961, 2011 – Annex 9: Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products). The document is available for download at http://bit.ly/34vnh30.

4. TEMPERATURE MONITORING DEVICES

4.1 Introduction

International shipments of vaccines must be in accordance with the recommendations established by the vaccine manufacturer and agreed to by the logistics service provider in order to keep the product temperature within the defined range, as described by the manufacturer on the outer packaging. The acceptance of shipments with temperature excursions outside the defined storage temperature limits are addressed by the temperature alarm settings recommended by WHO in this chapter.

WHO PQS prequalified electronic data integrators (EDI) should be included in all boxes of vaccine shipments to document whether temperature allowance limits have been exceeded. These devices should:

1. serve as a crucial reference to help recipient countries determine whether the shipment – or parts of the shipment – have been exposed to temperatures at which vaccines could have been damaged, and
2. gather data that helps the procurement agency determine when, where and to what extent temperature allowance limits have been exceeded, so similar situations may be prevented in future shipments.

Electronic data integrators provide the most reliable and accurate record of temperature excursions.

In addition to the EDIs placed inside each shipping box mentioned above, manufacturers may decide to include one external data logger to be placed on the outer surface of the “index shipping box”. This data logger ensures that unusual shipping conditions (e.g. exposure to external conditions on airport tarmac) can be easily identified during the investigation of a shipment complaint. Furthermore, use of an external data logger in this way can help manufacturers to collect data for transport route profiling. This data logger must be robustly fixed to the index box in such a way as to prevent any detachment during the shipment. Before accepting a shipment, once inspection has been concluded the recipient should make sure that alarms have not been triggered on the monitoring devices. If there is an alarm in one or more of the devices, the recipient should contact the procurement agency for action and ensure affected vaccines are stored under the appropriate conditions and segregated under quarantine until further assessment of the impact on the vaccine.

Specific information obtained from the EDI devices (e.g. time of excursion, duration of excursion, minimum or maximum temperature measured during the excursion) is important for the purchasing agency, the manufacturer, logistics service provider and consignee. This information is used to identify the cause of the excursion so corrective actions can be implemented to avoid similar situations in future shipments as well as for insurance purposes.

4.2 Electronic data integrators for international shipments

WHO recommends that one electronic data integrator is included in each and every shipping container. For shipping containers exceeding 800mm in height, it is recommended that two devices should be used and positioned according to the cold and hot spots identified by thermal mapping.

EDIs must be started when vaccine is packed in tertiary package and must be capable of recording data for the planned duration until receipt with reasonable excess to account for logistical delays.

Diluents that are packaged separately are not required to have a temperature monitoring device except in the case where diluent is freeze sensitive. In this case each diluent shipping carton requires use of a device that can indicate exposure to freeze conditions. WHO PQS prequalified electronic freeze indicators could be used for this purpose.

WHO does not encourage manufacturers to use dry ice. If dry ice is used as coolant electronic data integrators cannot be used because extreme cold has a negative impact on the batteries. In such cases, a cold chain monitor (CCM) card may be used instead of a data integrator. WHO no longer recommends CCM for any other use.

Use of temperature monitoring devices powered by lithium batteries other than coin cells should be avoided (IATA 2017 Lithium Battery Guidance Document) as this would require shipments to be labelled as Dangerous Goods.

Table 3. Specifications of the electronic shipping indicators (electronic data integrators).

Operating temperature range	Upper limit +55°C, Lower limit -30°C
Accuracy	Temperature: ±0.5°C or better within the range -5°C to +25°C; ±1°C within the ranges -20°C to -5°C and +25°C to +55°C Time: ± 10 seconds per day or better
Resolution	±0.2°C or better within range -20°C to +55°C
Power source	Non-replaceable battery
Sensor	Electronic
Memory	EPROM or equivalent non-volatile solid-state memory device.
Product response time	T90 10 minutes maximum in accordance with EN12830.
Unit of measurement	°C
Calibration	Each product is to be covered by a Certificate of Traceability and Calibration.
Logging Interval	10 minutes or less
Logging start delay	60 minutes
Casing and IP rating	Casing non-corrodible plastic or metal, IP rating not less than IEC 60529: IP64
Minimum storage life (battery)	18 months before ‘start’.
Minimum recording period	40 days
Minimum data retention after ‘stop’	6 months
Electromagnetic compatibility	Compliant with IATA requirements
Ambient temperature range during transport and storage	-30°C to +55°C with device inactivated.
Ambient humidity range during transport, storage, and use	0% to 95% RH

These devices should, at a minimum, meet the specifications outlined in PQS performance specification for electronic shipping indicators, E006/TR07.3 as summarized in Table 3 above and have the following functions outlined below:

1. **Activation**: The device must be activated by the sender at the beginning of the recording period by means of a 'start' button or 'switch' mounted on the unit.
2. **De-activation**: The device must be de-activated by the receiver at the end of the recording period by means of a 'stop' button or a switch button mounted on the unit. If the 'stop' button or switch is not de-activated, the device should automatically default to the deactivated state at the end of the 40 day recording period, as applicable.
   The 'stop' button or switch should be designed to prevent inadvertent de-activation - for example by contact with a shifting load.
3. **Display**: The device is to have an LCD display screen, with or without LEDs. The display screen should be capable of showing the following information:
   a) Activation status.
   b) Post activation battery status, or clearly marked expiry date in the format of MM/YYYY.
   c) Overall alarm status: whether or not an alarm condition of any kind has occurred since the device was activated.
   d) Time-temperature alarm status: the status of each of the three time-temperature alarm thresholds specified in clause 4.2.12 of the WHO/PQS/E006/TR07-VP.3 PQS performance specification at the time when the 'stop' button is activated.
   e) Total elapsed transport time in days and hours, or in hours measured from device activation to device de-activation.
   f) Shipment history: A history of the shipment capable of showing details of at least one time-temperature limit violation for each alarm type including the first timetemperature violation of each alarm type.
   g) The display must be capable of being photocopied in order to provide hardcopy record of the status of the device upon arrival (no flashing or blinking symbols/lights).
4. **Optional**: A USB interface or equivalent wireless interface to download a time-temperature data graph in PDF format obtained by plug-in and without the need for the user to download special software.

The following tables display WHO PQS-prequalified EDIs of different types, with set high and low temperature alarms. Type 1 and type 2 devices are now renamed 'A', 'B', or 'C', in line with the packaging type. Device manufacturers are requested to adopt the new naming convention at the latest 31 December 2021 (so they may exhaust their stocks with printed Type 1 and Type 2 stickers).

Table 4. Type A/B – previously called Type 2: WHO-recommended alarm settings for international shipments of OPV, BCG, Hib lyophilized, influenza seasonal (lyophilized), JE lyophilized, measles, MR, MMR, meningococcal A, meningococcal ACYW 135 (lyophilized), rabies (lyophilized), rotavirus (Bharat liquid and lyophilized – other than RotaTeq), rubella, varicella, yellow fever.

Temperature	Alarm type	Period for triggering the alarm
High threshold	>= 45°C single event	1 hour
Medium threshold	>= 30°C cumulative exposure	10 hours
Low threshold	>= 10°C cumulative exposure	20 hours

Table 5. Type C – previously called Type 1: WHO-recommended alarm settings for international shipments of DTP, DT, DTP-HepB-Hib, Hib (liquid), HepA, HepB, HPV, Influenza seasonal (liquid), IPV, JE (liquid), Meningococcal ACYW-135 (liquid), OCV, PCV (other than Prevnar), Rabies, RV (liquid and other than Bharat liquid), TT, Td.

Temperature	Alarm type	Period for triggering the alarm
High threshold	>= 45°C single event	1 hour
Medium threshold	>= 30°C cumulative exposure	10 hours
Low threshold	<= -0.5°C single event	1 hour

Table 6. Type RotaTeq: WHO-recommended alarm settings for international shipments of Rotavirus vaccine from manufacturer Merck Sharp and Dohme.

Temperature	Alarm type	Period for triggering the alarm
High threshold	>= 27°C single event	1 minute
Medium threshold	>= 17°C cumulative exposure	2 hours
Low threshold	<= -25°C single event	1 minute

Table 7. Type Prevnar: WHO-recommended alarm settings for international shipments of pneumococcal vaccine from manufacturer Pfizer.

Temperature	Alarm type	Period for triggering the alarm
High threshold	>= 40°C single event	1 hour
Medium threshold	>= 30°C cumulative exposure	10 hours
Low threshold	<= -0.5°C single event	1 hour

4.3 Shipment information card

1. Each electronic device should be mounted on a moisture resistant backing card, using moisture resistant adhesive. The card material must accept indelible markings in ball point pen. The width of the card must be at least the same as the length of the device, subject to a minimum width of 7.5cm. The length of the card must not exceed 14cm. The card design must follow the generic format and colours set out in *Annex 3* (yellow for Type C and Prevenar®, blue for Type A/B and Rotateq®). User instructions must be available either in English, French or Spanish language, as requested by the customer. Text must be in a high legibility font – minimum 8 point, colour black.
2. Shipment information card must include information on the type of device and instructions for the sender on the front face along with information on shipment, and instructions for the receiver on the back face.
3. For all details of the cards refer to *Annex 3*.

The below tables provides instructions for the receiver about the actions to take in the case of alarm.

Table 8. Information to be displayed on the backing card of electronic device – (Type A/B - previously called Type 2) for international shipments of OPV, BCG, Hib lyophilized, influenza seasonal (lyophilized), JE lyophilized, measles, MR, MMR, meningococcal A, meningococcal ACYW 135 (lyophilized), rabies (lyophilized), rotavirus (Bharat liquid and lyophilized – other than RotaTeq), rubella, varicella, yellow fever.

Alarm temperature	What to do with vaccines	
	OPV	Other vaccines
>=45°C	Contact procurement agency	Contact procurement agency
>=30°C	Contact procurement agency	Contact procurement agency
>=10°C	Contact procurement agency	Accept

Table 9. Information to be displayed on the backing card of electronic device – (Type C – previously called Type 1) for international shipments of DTP, DT, DTP-HepB-Hib, Hib (liquid), HepA, HepB, HPV, Influenza seasonal (liquid), IPV, JE (liquid), Meningococcal ACYW-135 (liquid), OCV, PCV (other than Prevnar), Rabies, RV (liquid and other than Bharat liquid), TT, Td.

Alarm temperature	What to do with vaccines
>=45°C	Contact procurement agency
>=30°C	Contact procurement agency
<=-0.5°C	Conduct shake test. USE vaccine if passes. Inform procurement agency of test result

Shake test protocol and sampling methodology are given in *Annex 4* and *Annex 5*.

Table 10. Information to be displayed on the backing card of electronic device (Type Rotateq) Rotavirus vaccine from manufacturer Merck Sharp and Dohme.

Alarm temperature	What to do with vaccines RotaTeq only
>=27°C	Contact procurement agency
>=17°C	Contact procurement agency
<=-25°C	Contact procurement agency

Table 11. Information to be displayed on the backing card of electronic device (Type Prevnar) pneumococcal vaccine from manufacturer Pfizer.

Alarm temperature	What to do with vaccines Prevnar only
>=40°C	Contact procurement agency
>=30°C	Contact procurement agency
<=-0.5°C	Conduct shake test. USE vaccine if passes. Inform procurement agency of test result

4.4 The impact of high temperatures on the stability time of vaccines, as indicated by high temperature alarms

Although international shipping containers are qualified by vaccine manufacturers using transport route profiles targeting the label temperature range, WHO allows certain temperature exposures beyond the 8°C based on the vaccine stability budgets.

Impact of packaging type on temperature excursions

A/B type packaging

A/B type packaging uses frozen icepacks (or dry ice in some cases), because this category packaging includes OPV and only other vaccines that are not affected by freezing. In principle, the temperature in the vaccine load section of the container is always at negative degree Celsius in the beginning of the shipment. As a result, there is a very low probability of a high temperature alarm with this category packaging. Exceptional circumstances may include a final shipment duration that is much longer than it is planned or that the cargo is stuck due to an unexpected strike or a grave mishandling (placing the cargo behind the jet stream prior to loading to aircraft).

C type packaging

The vaccine load of the shipping container is at 2-8°C in the beginning of the shipment. High temperature alarms are therefore more likely compared to class A/B type packaging.

Important: All alarms should be reported to the procurement agency. Depending on the number of instances that an alarm is triggered and the severity, the procurement agency may advise to accept or reject the shipment.

Calculating stability time expiration

Based on the given temperature history, stability time expired is calculated in percentage if the vaccine is to be kept at 37°C (and 55°C for 250 days stability).

Step 1 – calculate 'days remaining'

Days left = Stability time–length of transport in days*EXP(-Temperature dependence*(1/MKT)-1/(Spec Temperature))

where;

- **Stability time** is the expected time when 95% of the temperature integrators (TTIs) should reach their end point at 37°C (2 days for VVM2, 7 days for VVM7, and so on).
- **Temperature dependence** is the activation energy of the time and temperature integrator (TTI) divided by the gas constant R.
- **MKT** is the mean kinetic temperature, which is the single temperature that would have the same effect on the TTI as the actual temperature history.
- **EXP** is the exponential function.

Note: Temperatures are expressed in °Kelvin, which is°C + 273.

Step 2 – calculate 'stability time expired'

Stability time expired (in percentage) = (stability time-days left)/stability time

Indicative examples of the impact of high-temperature on vaccine stability

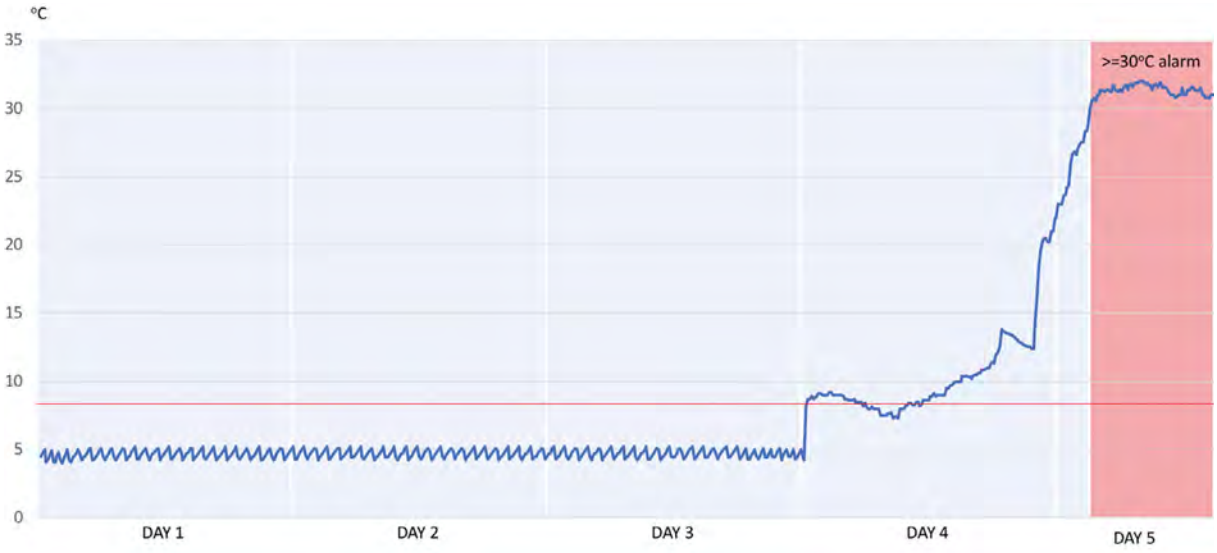
Three temperature recording data scenarios are provided here as examples to illustrate the impact of high-temperatures (indicated by alarms) on the stability time of different vaccines. Complete temperature data points are provided in *Annex 6*.

Vaccines are categorized into six groups based on their stability time at 37°C, measured in days. The stability of the same type of vaccine from different manufacturers may be different and, as a result, the following scenarios only indicate the stability characteristics of vaccines at 37°C without mentioning the type of vaccine. If the vaccine has a VVM, users may refer to the VVM to verify the stability group of that vaccine. This information is either printed on the outer circle of the VVM or outside (i.e. VVM2, VVM7, VVM11, VVM14, VVM30, and VVM250), as shown in Figure 5 below.

Figure 5. How to find vaccine stability characteristics with the help of VVM.

This information can also be checked at product pages of WHO prequalified vaccines at http://bit.ly/2L7Vxty.

Scenario 1



Minutes per measurement	10					
Total transit time	4 days 14 hours 24 minutes					
Minimum temperature	4.0°C					
Maximum temperature	31.9°C					
Average temperature	9.4°C					
MKT	18.5°C					
Time over 8°C	35 hours 00 min					
Time >= 30°C	11 hours 50 min					
Stability time at 37°C in days	**2**	**7**	**11**	**14**	**30**	**250**
Stability time expired (percentage)	15.97%	4.02%	2.56%	2.01%	0.94%	0.12%

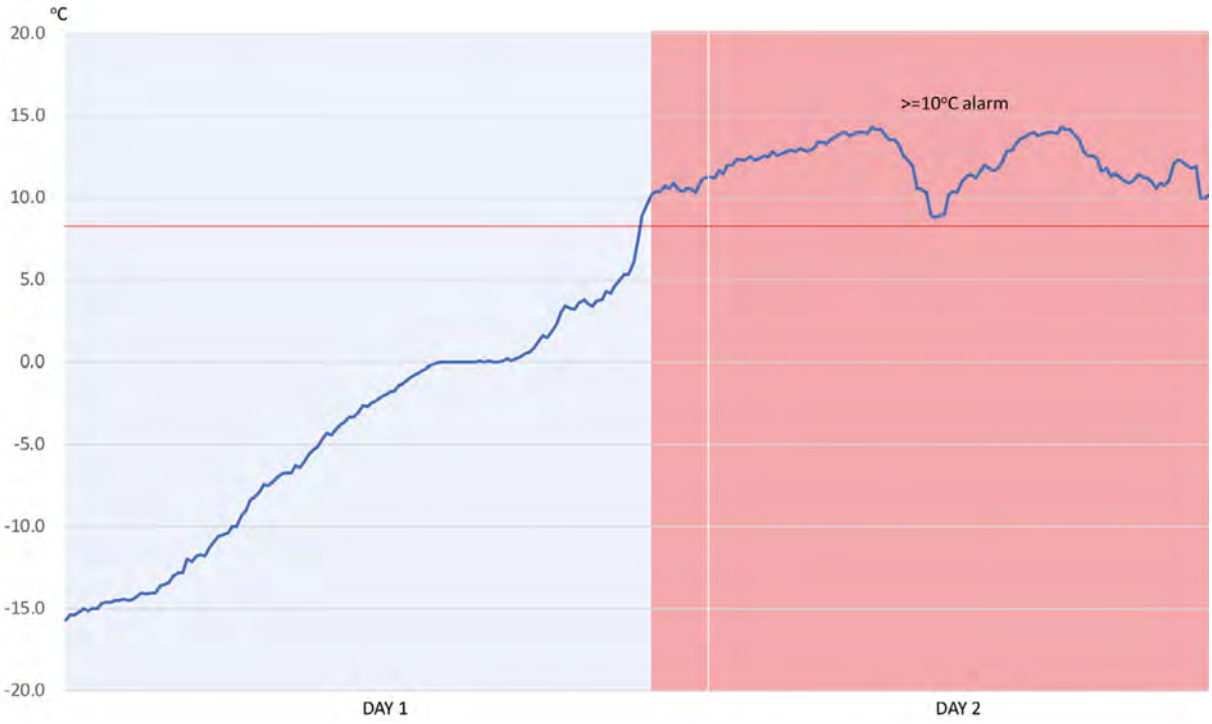
Although all vaccines are included in the analysis it would not apply to class A&B packaging because in most cases type A&B packaging incorporates frozen icepacks as coolants and, as a result, internal temperature of the shipping container is always at negative degree Celsius when the container is sealed. OPV is never shipped without icepacks. However, in some cases it is shipped with dry ice. Despite indicating life lost for 2 days stability at 37°C (all OPVs), this would not apply to OPV. For other vaccines that are not affected by freezing, if they are packed like class C packaging, this scenario would be applicable.

Scenario 2

Minutes per measurement	10					
Total transit time	2 days 30 minutes					
Minimum temperature	4.2°C					
Maximum temperature	15.9°C					
Average temperature	9.2°C					
MKT	10.0°C					
Time over 8°C	32 hours 30 min					
Time >= 30°C	21 hours 49 min					
Stability time at 37°C in days	**2**	**7**	**11**	**14**	**30**	**250**
Stability time expired (percentage)	2.20%	0.44%	0.28%	0.22%	0.10%	0.01%

This scenario would also not apply to OPV. For all other vaccines, the impact of the temperature exposure on shelf life is less than 0.4%.

Scenario 3



Minutes per measurement	10					
Total transit time	1 day 18 hours 40 minutes					
Minimum temperature	-15.7°C					
Maximum temperature	14.3°C					
Average temperature	3.6°C					
MKT	8.6°C					
Time over 8°C	21 hours 20 min					
Time >= 30°C	20 hours 20 min					
Stability time at 37°C in days	**2**	**7**	**11**	**14**	**30**	**250**
Stability time expired (percentage)	1.50%	0.30%	0.19%	0.15%	0.07%	0.01%

This scenario would apply to Class A/B packaging. For OPV the impact of the temperature exposure on shelf life is only 1.5%. For all other vaccines the impact is less than 0.3%.

In all cases, the procurement agency needs to be contacted with the details of the alarm. Depending on the number of alarms, severity and the type of vaccine, the procurement agency will inform the recipient country on the outcome of the evaluation to whether accept or reject. In the case of rejection, it applies only to the shipping containers with the mentioned alarm, the shipping containers with no alarm from the same shipment cannot be rejected.

4.5 Temperature excursions with no alarm

In devices with download feature (USB interface), the extent of any temperature limit violations can be seen, even if no alarm is triggered. In such cases, the highest temperature reached and the violation duration will be visible. This is an important feature and the data should be communicated to the procurement agency for evaluation in order to ensure that the correct measures may be taken to prevent similar cases in the future.

Regardless of the duration of the violation (that in all cases below the time limit of the mentioned alarm), if there is no alarm, these products should be accepted.

4.6 Interpreting VVM in international shipments

Electronic data integrators are designed to monitor temperatures during transit. VVMs are not designed as shipping indicators and although they are required to be checked upon arrival, they are not used to evaluate the temperature exposures during an international shipment. It should be noted there that a VVM's active surface (the square) is never white; in general, the square of the VVM is about 5-10% tinted with the colour of the reference ring.

All possible below:

- If there is no alarm, a VVM can have no status change. Even if no change in the status in VVM is expected, VVMs must still be checked to record the findings in the arrival report.
- In the case of an alarm for a temperature of <=-0.5°C, there cannot be a VVM status change. A VVM does not change colour at negative temperatures.
- An alarm for a temperature of >=10°C is important for OPV. In the case of an alarm of >=10°C for vaccines other than OPV the shipment should be accepted. A VVM does not produce a visible status change with any of the vaccines at this level of temperature excursion for the duration of the shipment.
- In the case of an alarm for a temperature of >=30°C shipment may be rejected depending on the number and severity of the high alarms, subject to confirmation by UNICEF and/or WHO HQ. In most of these cases, the VVM status will not be compromised. However, depending on the number and severity of the higher temperature alarms, the VVM status change may be evident by visual inspection.
- In the case of an alarm for a temperature of >=45°C shipment should be rejected. Depending on the number and severity of the temperature excursion the VVM status change may be evident by visual inspection.

In principle, when there is no alarm it is very unlikely that a VVM will be observed to have changed versus its start-point. If a VVM is observed to have changed in the absence of a temperature excursion alarm it can be for one of (only) three reasons:

- **The electronic shipping indicator is faulty** – In this case the recipient country must analyze the transit time, connections and coolant status on arrival.
- **The VVM(s) was mishandled before being attached to the vaccine(s) at the manufacturer's facility** – This has not been observed since the introduction of VVM in 1996; however, it is a theoretical possibility. If it were to happen it could be established by a simple investigation. Requesting retained samples, release reports, and acceptance reports of the VVM batch in question from VVM manufacturer and the vaccine manufacturer in order to make a direct comparison of the results would help to determine whether this is the case. The investigation could be conducted by WHO.
- **The vaccines were stored for longer periods of time before shipment at the manufacturer's facility** – If the labelled vaccines (with VVMs attached) are kept for long periods of time at the manufacturers storage facilities they will be affected by time and temperature (even when maintained at 5°C at all times). However, this may also result in the distribution of vaccines with short expiry dates which may be another ground for rejecting the shipment. This could also be established through a WHO investigation.

5. VOLUME PER DOSE AND BULKING FACTORS FOR CALCULATING NECESSARY STORAGE

The storage volume per dose of vaccine varies according to the type of vaccine, the number of doses per vial or ampoule, the dimensions of the primary container and the secondary packaging. Countries that receive their vaccines through UN agencies do not know in advance which vaccines they will receive. This presents a challenge for countries to estimate their cold-chain requirements.

Some countries also store vaccines in pallets and/or in their tertiary packages at the primary level. It is therefore important for countries to know the bulking factors for tertiary packages in order to calculate their storage requirements.

The WHO vaccine prequalification list is regularly updated and changes made to its contents. As a result the list of volumes per dose and bulking factors for tertiary packages is not provided in this *guideline* document. Instead, WHO offers a spreadsheet that is maintained up to date in line with the vaccine prequalification list, available for download here: https://tinyurl.com/y2wopnrb. It should be noted that these figures correspond to dimensions of actual prequalified products. In all calculations, for safety reasons, the worst-case scenario with the largest volume should be used.

The Vaccine Presentation and Packaging Advisory Group (VPPAG) of WHO recommends the following packaging rules to vaccine manufacturers in order to minimize volume per dose of vaccines.

For primary containers (vials)

- Vaccines in presentations from one to five 0.5-ml doses are recommended should be filled in a “2R” vial conforming to ISO (International Organization for Standardization) 8362 dimensions. Where technically possible, and if the dose size permits, manufacturers are encouraged to reduce the height of the vial from the current standard of 3.5 cm to 3.1 cm or less, both for reasons of volume reduction and dimensional harmonization.
- Vaccines in presentations of six to ten 0.5-ml doses should be filled in a “4R” vial conforming to ISO 8362 dimensions.
- Vaccines in presentations of twenty 0.5-ml doses should be filled in a “10R” vial conforming to ISO 8362 dimensions.
- For vaccines with a dose size less than 0.5ml the most compact of these three vial sizes should be used, depending on the number of doses in the presentation.
- It is recommended that for vaccines with a dose size greater than 0.5ml, the most compact of these three vial sizes be used, depending on the number of doses in the presentation.

Where possible, if changes are to be made to an existing prequalified vaccine product (e.g., changes in formulation or production that require regulatory resubmission), it is recommended that manufacturers select a primary container size that conforms to the relevant recommendation set out above.

For secondary packages

It is recommended that secondary cartons should contain vials in one or more of the following formats:

- 10 vials in an array of 5x2 vials,
- 25 vials in an array of 5x5 vials,
- 50 vials in an array of 5x10 vials,
- 100 vials in an array of 10x10 vials.

It is recommended that vials be packed in rectangular arrays, based on the above recommendations. The dimensions of the secondary carton should be the minimum necessary to accommodate the vials and the package insert, together with any internal dividers and subject to any necessary tolerances.

Appropriate justification should be provided if the secondary carton arrangements differ from the above recommendations.

For tertiary packages

It is recommended that:

- secondary cartons be packed into fibreboard tertiary cartons. The dimensions of the tertiary carton should be the minimum necessary to accommodate the chosen number of secondary cartons, subject to necessary tolerances,
- the total number of vials packed in a tertiary carton be a multiple of 100 vials so that the contents are easy to count,
- the gross weight of a tertiary carton not exceed 25kg and should preferably be no greater than 10 kg,
- the width dimension of the tertiary carton not exceed 45cm,
- tertiary carton dimensions be selected so that cartons can be efficiently stacked on standard ISO pallets with dimensions of 1.2 m x 0.8 m and/or 1.0 m x 1.2 m without overhanging the pallet footprint,
- tertiary packaging should be properly qualified to support the anticipated load.

Appropriate justification should be provided if the tertiary cartons differ from the above recommendations.

6. LABELLING FOR INTERNATIONAL SHIPMENTS

Providing information on multiple faces of a shipping container or package helps ensure products are identifiable during storage and distribution and helps to minimize product selection errors. It also promotes accuracy during routine stock management activities, such as stock counts.

It is recommended that tertiary shipping containers be labelled on at least two opposing faces, with a preference for three opposing faces. The printed content can consist of static information only. Dynamically applied information such as bar codes and serialization data may be on one face only.

6.1 Labelling for secondary packaging

A label must be affixed either to the top and/or front surface of the secondary package. It should indicate the type of vaccine, the name of the manufacturer, presentation, batch number, date of expiry, quantity and storage conditions. As an alternative to the label, a direct print can also be made on the secondary package. Labels for secondary packaging of both diluents and droppers must also indicate the above details.

6.2 Labelling for grouping case

A label must be affixed either to the top and/or front surface of the grouping case. It should indicate the type of vaccine, the name of the manufacturer, presentation, batch number, date of expiry and storage conditions.

6.3 Labelling for shipping container

The external surface of insulated shipping container should be either white or in the natural colour of corrugated carton. Dark colours must be avoided.

A label must be affixed to two opposing faces of each shipping container indicating the type of vaccine, name of manufacturer, presentation, batch number, date of expiry, quantity and storage conditions.

Expiry date on all labels should be written in MM.YYYY format (e.g. 06.2022).

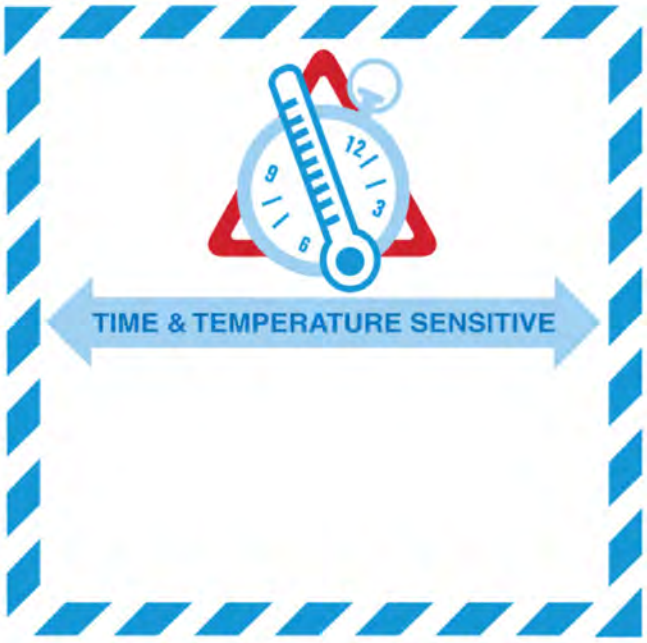
Required temperature conditions for transportation must be clearly visible on the outer carton. All labels on shipping containers must be placed in a way so it does not cover the seam of the carton. If placed on the seam, the label could be damaged when the carton is opened or bar codes could be distorted by the seam.

6.4 IATA time and temperature sensitive label

In addition to the static information (and possibly dynamic information) there are other labelling requirements that must be met. Mandatory from July 2012, the IATA Time and Temperature Sensitive Label is a shipment label specific to the healthcare industry that must be affixed to all shipping units booked as time and temperature sensitive cargo. It is the responsibility of the manufacturer to ensure the label is applied properly to each shipping unit indicating approved transportation temperatures, and in accordance with IATA Guidelines. The required temperature range should be indicated on the lower half of the label. The temperature range indicated on the label always reflects the temperature external (or ambient temperature) to the package allowed during transportation and distribution and not the actual product (internal) temperature.

It is not permitted to leave the lower half of the label blank. In the event that the shipper fails to complete the lower half of the label or, in case of discrepancy, the transportation temperature indicated on the Airway Bill (AWB) prevails.

Figure 6. IATA time and temperature sensitive label.



The label must be affixed to at least one side panel of the outermost visible means of containment. Labels on packages within a palletized shipment must be clearly visible or else be reproduced on the outer package. Shipments that require to be split or broken down should have labels applied to every outer package. Where diluents and droppers are required to be stored at ambient temperature, they can be booked at +2°C to +8°C for the practical reason that they are shipped with the vaccine on the same AWB. IATA regulations do not allow two or more different temperatures on the same AWB.

For further details on the IATA time and temperature sensitive label, refer to https://www.iata.org/contentassets/6d7404d9ccca4e4e9c4ce146e4a2acb1/time-temperature-faq.pdf.

When dry ice use is unavoidable as a coolant, labelling and marking should be in accordance with IATA Dangerous Goods Regulations. Class 9 hazard label must be applied to containers with dry ice. UN1845 is the numeric identifier for dry ice assigned by the United Nations and the UN Committee of Experts on the Transport of Dangerous Goods.

Figure 7. Class 9 hazard label for dry ice shipments.

6.5 “Do Not Freeze” label

The IATA time and temperature label must only to be used to indicate the transport temperature (or SOP number) for shipments booked as temperature controlled. Any other instructions should be placed outside of the label. These instructions should not conflict with the instructions on the IATA label and must be agreed to by all parties involved.

WHO requires manufacturers to affix an additional label of “Do Not Freeze” on the front and rear face of the containers of freeze-sensitive vaccine shipments in the language agreed. Containers with freeze-sensitive diluents and OPV droppers where droppers are at risk of being damaged by freezing should also be affixed with “Do Not Freeze” label.

6.6 Index box (Number 1 container with shipping documents)

All insulated shipping containers should be numbered consecutively and box numbers shall not be repeated for shipments containing boxes of droppers or diluents shipped in the same consignment as vaccines.

Shipping documents should be included in the box labelled # 1, and this box should be clearly labelled with the words “Containing vaccine shipping documents”.

Manufacturers should indicate on the outer carton where boxes are not stackable or maximum stacking height, where applicable.

6.7 Barcoding

Barcodes are used to encode information such as product numbers, serial numbers and batch numbers. Barcodes play a key role in supply chains, enabling parties like retailers, manufacturers, transport providers and hospitals to automatically identify and track products as they move through the supply chain.

WHO does not currently require barcodes but vaccine manufacturers should comply with GS1 standards and associated specifications if used.

For new tenders issued after 1 October 2019 and to be implemented as of 31 December 2021 at the latest, UNICEF is requiring barcodes to be implemented at all levels except for the primary level in accordance with WHO guidelines on programmatic suitability.

7 INTERNATIONAL SHIPPING PROCEDURES

The arrival of a vaccine shipment in a country, its subsequent clearance through customs and transportation to the central vaccine store are the most critical stages in the shipping process. These are frequently the times when mistakes and delays occur, resulting in damage to the vaccines. The smooth arrival and handling of vaccine shipments depends on the way each step in the delivery process is performed. Numerous parties are involved (procurement agency, other UN agencies, the manufacturer, the forwarder, the airline, the UN country office, customs authorities, clearing agents, or the national immunization service), and because of the need to communicate accurate, time-sensitive information, it is essential to have strict guidelines to determine and assign responsibilities at every step of the process. These are described in the general terms and conditions of the tender documents and are further detailed in individual contracts. The specific conditions depend on the country of destination.

7.1 Temperature control during international transportation

Vaccines must always be kept in temperature-controlled environments throughout the shipment process including in transit storage points or warehousing.

All vaccines must be booked and shipped at +2°C to +8°C, or as specified by manufacturer. Specified temperature range for transport must be indicated on the IATA time and temperature sensitive label.

It is prohibited to send vaccines or diluents by general cargo. Shipment of droppers as general cargo must be agreed in advance with the UN agency and manufacturer.

Vaccines must not be transported with radioactive products, pesticides, fertilizers, fish or meat.

Re-icing of shipments must be performed in accordance with the written instructions of the manufacturer of each shipment whenever deemed necessary.

7.2 Route and arrival dates

Vaccines should travel by the fastest and most direct route wherever possible. Where transshipment is unavoidable, the journey should be planned through airports that have adequate cold storage facilities. Shipment must be dispatched as booked unless approved in writing in advance by UNICEF, PAHO and/or other UN agencies.

If the route deviates significantly from the standard routing, or delays are expected, the logistics service provider (LSP) or freight forwarder shall contact the UN agency in advance. Shipments should be scheduled to arrive outside weekends and/or public holidays in the recipient country unless agreed in advance by the UN agency and airline bookings should be made well ahead of the date of departure and as specified by the UN procurement agency. Any additional requirements regarding arrival times must be stated in the contract between UNICEF and/or the other UN agencies or manufacturers and the designated freight forwarder. Consolidation or splitting of consignments is not permitted unless approved in advance by the UN agency.

7.3 Advance shipment arrival notification

It is the obligation of the LSP or freight forwarder to inform the consignee and all requested "notify parties" of all shipment details in advance of the shipment, in a format pre-defined by the UN agency. Required documentation for the shipment must be sent at least seven days (to include at least five working days) in advance of arrival of the shipment, or as otherwise specified by the UN agency.

The documentation must include the following:

- pre-advice cover page as defined by UNICEF, PAHO and/or the other UN agencies,
- Airway Bill (AWB),
- supplier's invoice,
- packing list/packing slip correlating information of electronic shipping devices with the insulated shipping unit (PAHO),
- lot release certificate (LRC) issued by the national regulatory authority (NRA) of the country of manufacture[1] for each lot of vaccine supplied, and
- any other document, certificate or instruction specified in the purchase order.

[1] There might be cases where lot release certificate is not issued for each final lot, such as US FDA not providing a certificate for each final lot of Menactra (meningococcal conjugate) but certifies release at the bulk level.

The documents should be sent by e-mail by the LSP or freight forwarder to the consignee, the UNICEF, PAHO or UN agency country office in the receiving country, Vaccine Centre, UNICEF Supply Division for UNICEF shipments and any other parties specified in the individual contract.

The pre-advice must contain the following information:

- purchase order reference,
- consignee requisition reference,
- number of packages, gross weight (in kilograms) and volume (in cubic metres),
- type of vaccine, total number of primary containers and number of doses per primary container,
- value of shipment (in US$),
- AWB and flight number(s),
- date and time for place of departure, transit (if applicable) and arrival,
- instructions for collection,
- any other information specified in the purchase order must also be included for the consignee.

The following information shall be stated on the AWB:

- consignee's name, address and telephone number,
- purchase order reference,
- consignee's requisition reference,
- type of vaccine and quantity,
- instructions to: "Telephone consignee upon arrival (repeat telephone number)",
- handling information: "Vaccine – For human use – Highly perishable – Not to be delayed".

For all vaccines the required temperature range should be stated tin the AWB. This should match with the temperature range indicated on the IATA time and temperature sensitive label. In the case of conflict, handling staff are obliged to comply with the range indicated in the AWB. It should be noted that IATA does not allow more than one temperature range in an AWB.

House Airway Bills (HAWB) are not permitted unless approved in writing in advance by UNICEF, PAHO and/or other UN agencies.

Vaccines are not to be advance shipped or arrive earlier than notified ETA.

Insulated shipping containers are not to be opened in transit by the LSP/ freight forwarder, with the exception of the requirement for re-icing as agreed with the manufacturer. Electronic devices are not to be stopped by the LSP/ freight forwarder until receipt by consignee in recipient country, unless otherwise agreed by UNICEF/PAHO/UN agency.

If any shipment incurs loss or damage during transit, the LSP/freight forwarder, manufacturer, or consignee shall inform UNICEF, PAHO or UN agency immediately to provide the shipment details and the estimation of the loss and damage to initiate the insurance claims process.

7.4 Documents that accompany shipment

The following original documents must accompany the consignment when it is shipped. One set of the following original documents must also be placed inside the index shipping box numbered "1". Different UN agencies may require different documents to accompany shipments.

Table 12 lists the documents required by UNICEF and PAHO to accompany shipment.

Table 12. Documents that must accompany shipment (UNICEF and PAHO)

Document	UNICEF	PAHO
Airway bill	YES	YES
Supplier's invoice	YES	YES
Packaging list	YES	YES
Lot release certificate[2]	YES	YES
Lot summary protocol	YES	YES
VAR (blank)	YES	-
Insurance certificate	-	YES
Certificate of origin	-	YES
Certificate of pharmaceutical product (CPP)	-	YES
Free sale certificate (FSC)	-	YES
Certificate of analysis	-	When applicable
Any other document, certificates or instructions specified in the purchase order.	YES	YES

The index shipping box containing the documents should be clearly labelled with the words "Containing vaccine shipping documentation".

The lot release certificate(s) from the NRA (or from the national control laboratory) of the producing country should be included for each lot contained in the shipment. The LRCs are considered to be the only evidence that the lots received have been released by the regulatory authority of the producing country. Vaccines delivered without a lot release certificate cannot be accepted and must be kept on hold under appropriate storage conditions. In such cases, the LRCs should be provided immediately by the manufacturer.

[2] There might be cases where lot release certificate is not issued for each final lot, such as US FDA not providing a certificate for each final lot of Menactra (meningococcal conjugate) but certifies release at the bulk level.

7.5 Reporting arrival of vaccines

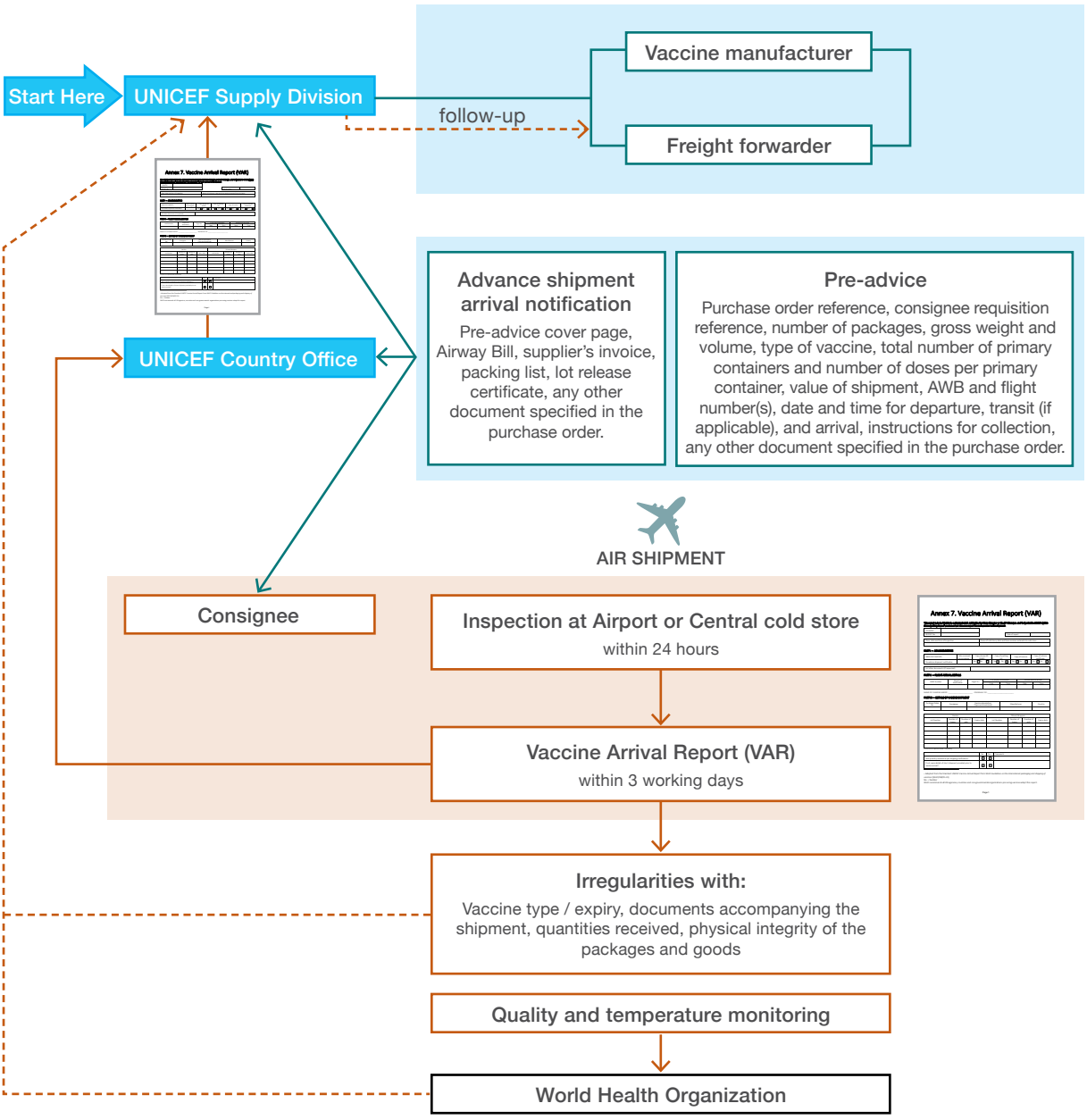
In principle, the recipient party of an international shipment should issue an arrival report to document the status of the goods to facilitate either acceptance or documenting any inadequacies in the shipping process and problems relating to the condition of the goods at the time of delivery that may result in rejection. The vaccine arrival report (VAR) referred in this section is a report used in UNICEF vaccine shipments. PAHO requirements for documentation of arrival of vaccines differ from UNICEF. Although UNICEF VAR may contain specific information required by UNICEF, the general logic of such arrival reports remain similar.

VAR is a means of monitoring international shipments of vaccines in order to ensure that shipping guidelines are followed and that vaccine quality is maintained. The VAR provides a means of indicating any shortfalls and failures in the shipping process and problems relating to the condition of vaccines at the time of delivery (*see Annex 7*). Recipient governments are responsible for issuing the VAR. UNICEF and/or WHO officers should support the recipient governments to ensure that the VAR is duly completed by authorized staff from the Ministry of Health (e.g. logistics manager, cold chain manager, cold store manager), checked and verified by the immunization programme manager and forwarded to UNICEF Country Office (who will subsequently forward to UNICEF Supply Division) within three working days of the arrival of the vaccine. In the case of combined shipments, a separate report should be filled in for each vaccine type in the shipment.

For countries receiving vaccines through UN agencies, all complaints should be sent immediately to the local country office of the procurement agency for them to follow up with their procurement organization. Depending on the nature of the complaint, the procurement agency may handle the issue itself or may request assistance from WHO. For countries procuring vaccines directly, all complaints should be handled directly with the vaccine manufacturer. WHO assistance can, however, be sought if required, for WHO prequalified vaccines.

Figure 8 illustrates pre-shipment and vaccine arrival report processes for vaccines procured by UNICEF. These procedures may be adapted for other procurement routes.

Figure 8. Pre-shipment and vaccine arrival report processes for vaccines procured by UNICEF



Any defect in the process can lead to a complaint, claim and/or rejection of a shipment. Each individual situation will be investigated and dealt with by all involved parties.

If the quantity of damaged vaccine is substantial it could affect immunization delivery. In such cases, emergency measures will have to be taken to obtain sufficient vaccine to maintain the programme's scheduled activities.

The forms (confirmation of arrival of shipments and claim report) used by PAHO are provided in *Annex 8* and *Annex 9*.

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ANNEX 1.

SUPPLEMENT 14

TRANSPORT ROUTE PROFILING QUALIFICATION

TECHNICAL SUPPLEMENT TO WHO TECHNICAL REPORT SERIES, NO. 961, 2011.

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products.

May 2015

CONTENTS

ABBREVIATIONS

CCP	critical control point
EDLM	electronic data logging monitor
ISTA	International Safe Transit Association
PDA	Parenteral Drug Association
TTSPP	time- and temperature-sensitive pharmaceutical product

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GLOSSARY

Ambient temperature

The uncontrolled prevailing temperature(s) within a specific environment or series of environments, such as a supply chain.

Conditioned ice-pack

An *ice-pack* that has been allowed to warm at ambient temperature until some liquid water is present inside the pack. The pack is correctly conditioned as soon as the ice core is able to move inside the pack when it is shaken. The effective temperature of a *conditioned ice-pack* in this state is 0.0°C.[1]

Cool life (test)

The empty passive container is stabilized at +43.0°C and loaded with cool water-packs which have been stabilized at +5.0°C for a minimum of 24 hours. Cool life is measured from the moment when the container is closed, until the temperature of the warmest point inside the storage compartment first reaches +20.0°C, at a constant ambient temperature of +43.0°C.[1]

Cool water-pack

A water-pack cooled to a temperature of +5.0°C before use.[1]

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 an acceptable or critical level. In the context of distribution and handling of time- and temperature-sensitive health-care products, CCPs 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.

Design qualification (DQ)

The process of obtaining and documenting evidence that the premises, equipment and supporting systems and processes have been designed in accordance with the requirements for good manufacturing practices (GMP).[2]

Electronic data logging monitor (EDLM)

A small portable device that measures and stores temperature at predetermined 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.

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*.

Ice-pack

A water-pack that has been frozen to a temperature between –5.0°C and –25.0°C before use.[1]

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.

Lanes

Transport routes from a point of origin to a destination.

Operational qualification (OQ)

The process of obtaining and documenting evidence, under controlled conditions, that the premises, equipment and supporting systems operate in accordance with their design specifications.

Passive systems

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

[1] Source: WHO Performance, Quality and Safety (PQS).
[2] WHO Technical Report Series, No. 961, 2011. Annex 3: WHO good manufacturing practices for pharmaceutical products: main principles.

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.[3]

Qualification protocol

A written and approved plan detailing how a qualification will be conducted including test parameters, product characteristics, equipment and acceptance criteria.

Qualification

Action of proving that any premises, equipment and supporting systems work correctly and actually lead to the expected results. The meaning of the word *validation* is sometimes extended to incorporate the concept of qualification.

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.

Study protocol

A document detailing the scope, objectives and operational specifics of a series of tests or data collection (study) written and approved in advance of execution of the study.

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.

Temperature-controlled

Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

Time and temperature-sensitive pharmaceutical product (TTSPP)

Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

Transport temperature profile

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

Validation

Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria.[4]

Vented shipping box

A container used to house an EDLM in order to record ambient air temperatures during transport, designed and constructed to maximize the airflow between the outside and inside of the container during the transport period. The container may be an integral part of a product shipment. Alternatively, if shipped separately, its overall size and weight should be similar to the container(s) used for the product(s) which are being monitored – this will ensure that the same handling practices are used.

Warm life (test)

The empty passive container is stabilized at +18.0°C and loaded with *warm water-packs*, which have been stabilized at the same temperature for a minimum of 24 hours. Warm life is measured from the moment when the container is closed, until the temperature of the coldest point inside the storage compartment first reaches 0.0°C at a constant ambient temperature of –20.0°C.[5]

Warm water-pack

A water-pack typically stabilized at room temperature, up to a recommended maximum of +24.0°C. Warm-packs are used for the transport of freeze sensitive vaccines when the ambient temperature is below 0.0°C.

[3] Definition from WHO/QAS/08.252 Rev 1 Sept 2009. Proposal for revision of WHO good distribution practices for pharmaceutical products – Draft for comments.
[4] PDA Technical Report No. 39: Guidance for temperature controlled medicinal products: Maintaining the quality of temperature-sensitive medicinal products through the transportation environment, 2007.
[5] Source: WHO PQS.

1. INTRODUCTION

This technical supplement has been written to amplify the recommendations given in section 6.8.3 and 6.8.4 of WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.[6]

Understanding the environment through which a TTSPP must travel is essential for successful logistics operations, for package design, and for maintaining the quality of the pharmaceutical product during external distribution. The best way to understand the temperature hazards that may occur during external distribution is to collect actual temperature data from representative parts of the supply chain. This process dispels assumptions, and can reveal weaknesses, risks and trends within the transport system. This document describes a method for profiling transport routes which is simple to understand and to execute; it is based on an approach called the "heat under the curve" method. Other techniques can also be used, but these tend to be more complex.

Temperature information gathered from a route profiling exercise can be used to develop representative ambient temperature profiles for specific lanes, modes and durations of transport. Route profiling is a prerequisite for carrying out a statistically representative operational qualification (OQ) or performance qualification (PQ) exercise involving shipping containers and refrigerated vehicles.

This supplement should be read in conjunction with the companion Technical Supplements: *Qualification of shipping containers and Qualification of temperature-controlled road vehicles*.

What is qualification?

In the context of this series of Technical Supplements, *qualification* is an inspection and testing process used to establish that a piece of equipment or a physical installation is fit for purpose in the operational context within which it will be used. There are typically three stages in the process. Each stage must be fully completed before the next one begins.

Stage 1 (for equipment): Establish by laboratory testing under tightly controlled conditions that a specific item of equipment performs in accordance with the user requirements specification (URS). This is *design qualification*. While design qualification demonstrates compliance with the URS and associated test protocols; it does not prove that the equipment will be suitable in a specific operating environment because the URS and the test procedures are unlikely to reflect the full range of operating conditions.

Stage 1 (for installations): Establish by documented inspection and testing that an installation[7] that has been assembled in a specific location is fully in accordance with the URS and installation drawings. This is *installation qualification.*

Stage 2: Establish by further documented testing under controlled conditions that this equipment or installation is likely to perform as intended in the operating environment in which it will be used. This is *operational qualification.*

Stage 3: Carry out a final stage of documented testing to establish with a high degree of assurance that the equipment or installation, together with all associated systems, does indeed perform as intended under routine operating conditions. This is *performance qualification.*

[6] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf.
[7] The installation will typically incorporate components that have a design qualification.

1.1 Requirements

Regulators increasingly require pharmaceutical transport operators to document their shipping practices in a manner which shows that they fully understand their transport process and are able to maintain control over it. As part of the process of validating these practices, the PQ of shipping containers and refrigerated vehicles should be based on transport route profile(s) which reflect the real distribution environment in a statistically robust manner. Consequently, the initial route profiling exercise should be carried out before actual products are distributed.

1.2 Objectives

The objective of the Technical Supplement is to provide a step-by-step methodology for establishing the ambient conditions that a package (parcel or palletized products) will experience while it passes through the distribution network. It describes:

a. a comprehensive and systematic approach to monitoring temperatures in a distribution system;

b. a protocol for temperature data collection;

c. a method for converting these data into a representative transport route profile with multiple confidence levels;

d. a simple method for estimating the performance of prequalified containers, laboratory tested at constant ambient temperature(s), against an ambient temperature profile;

e. a method for determining representative distribution temperatures for the qualification of shipping systems.

1.3 Target readership

This document should be used by supply chain personnel who are responsible for evaluating the external distribution environment. It should also be read by those responsible for developing or qualifying shipping solutions that are able to address the environmental hazards that will be encountered within a distribution system.

2. GUIDANCE

The fundamental purpose of a transport route profiling study is to collect temperature data that accurately represent real distribution practice. For example: if 90% of all shipments are made between five destinations, the sampling plan must accurately reflect this fact. However, the quantity of data collected should not be so great that it makes data handling and data organization difficult, confusing or subject to error. Once a representative ambient profile has been derived it can be used to qualify a shipping system whose performance aligns with the specific operational context. This supplement sets out the data collection and data analysis process and describes a simple approach for matching a shipping system with a profile – the *degree-hour* method.

Generally speaking, the ambient temperature along a transport route should be sampled once every 10–30 minutes. Increasing the recording frequency improves the resolution of the final data analysis. However, the chosen recording interval is ultimately determined by the overall shipping time and the maximum number of data points that the electronic data logging monitor (EDLM) is capable of capturing.

The sample size should capture the full range of segment variability that occurs in each transport scenario. This includes:

- the range of different carriers used;
- methods of shipment (express versus standard service);
- shipment days;
- mode of transport (ground, air and/or ocean);
- point of origin;
- point of destination;
- seasons (winter and summer or hot season and cold season);
- hemispheric crossings.

The chosen sampling size should reflect the actual application and the practicality of collecting the data. In general, the more data that can be collected, the better, because this will give a more accurate picture of temperature hazards encountered in any given lane. A sample size of 30 trips on a given route over the course of a year is considered to be statistically valid. However such a large sample is not always practical and the decision to choose a smaller sample size for a specific lane is a matter of judgement.[8]

Routine temperature monitoring is a useful tool for finding out why variability occurs during transport. Consequently, once a transport route has been formally profiled, periodic monitoring should continue. This monitoring helps identify risks, process changes and other trending data that may not have been identified in the formal study and which may subsequently affect the performance of transport operations.[9]

2.1 Associated materials and equipment

The following materials and equipment are needed to collect the temperature data needed to profile a transport route:

- EDLMs capable of downloading recorded temperature data to a PC for subsequent analysis. The same EDLM model from a single chosen manufacturer should be used throughout the data collection process. All devices should be identically preprogrammed with the same specifications for data collection frequency, alarms and recording duration. This will greatly simplify data organization and statistical analysis.
- Vented shipping boxes (optional). These boxes are used to protect the EDLMs. If the purpose of the study is to model the small parcel environment,[10] vented boxes are the most representative way to mimic this form of distribution and the unique handling and exposure which occurs. Vented boxes provide better air circulation for sensing the ambient temperature.
- The necessary hardware, software, desktop application or hosted database to extract the data from the device.
- Excel® or other spreadsheet or analytical software capable of organizing and analysing large amounts of temperature data.

2.2 Study protocol

It is essential to write a comprehensive study protocol and have it approved before the study begins. The protocol should cover the scope, purpose and detail of all study procedures and should include the following:

a. **Identify the purpose(s) of the study:** These might include any of the following: creation of an ambient temperature profile; collection of temperature or humidity data; identification of weaknesses, gaps or risks in the distribution system; or qualification of a shipping method.

b. **Select the shipping lanes for the study:** Define the origin and destination points of the shipments based on actual distribution needs. Ideally, the destination points would be actual shipping destinations. Alternatively, select logistically similar locations which are better able to receive and return the EDLMs. For example, an office in the destination town might be a more reliable choice than the actual destination warehouse.

c. **Transport modes(s):** Clearly define the mode(s) of transport or shipping methods which are to be used for the study. For example: same-day road delivery; three-day road delivery; international air freight with road pick-up and drop-off; ocean freight.

d. **Define the EDLM logging interval:** This must be the same across all shipments in the study in order to provide equal weight for temperature banding when the data are analysed. The chosen interval should provide sufficient resolution to capture expected temperature fluctuations, without generating unnecessary data. Typically a 10–30-minute logging interval gives adequate resolution and allows identification of the different stages of handling and manipulation along the shipping lane.

e. **Determine study duration:** i.e. to cover winter, summer, and other seasonal variability. This is to collect data that represent extreme temperature conditions (cold or hot). Ideally, data should be collected all year round (52-week study), but this may not be possible in many cases.

f. **Determine the sample size:** The International Safe Transit Association (ISTA) recommends that at least 25 samples are obtained for each variable. i.e., season (hot or cold), mode of transport as defined in point c, and origin, as defined in point b. Always prepare extra shipments[11] in case some of the test packages do not reach their intended destination or devices are not returned. This generally happens to about 10% of the test shipments.

[8] There are currently no recognized tools or references to help with this.

[9] Note that periodic monitoring is not a substitute for a formal route profiling qualification process.

[10] The cubic size and weight of a package can make a significant difference to how it is handled and this can also significantly affect its exposure to temperature. A small parcel does not necessarily experience the same thermal environment as a pallet-sized container. This should be considered and accounted for when gathering temperature data.

[11] A “shipment” in this context is a representative sample of product distributed from a single point of origin to a single destination. In the case of a delivery round more than one shipment on the vehicle may be monitored in order to capture route profiling data for different drop-off points.

g. **Choose the study product:** Determine whether the study will use real shipments or simulated shipments. Real shipments represent actual shipments of real products. Simulated shipments use packages without actual products. This applies to both parcel-sized and palletized products.

h. **Appoint a study manager:** Designate the person responsible for carrying out the study and for analysing and reporting the results.

2.3 Carrying out the study

It is important to carry out the study in a systematic, well-planned manner. If participants are not informed in advance, EDLMs will not be collected at the destination points and the data they contain will be lost. Observe the following rules:

a. **Training:** All study participants must be trained in advance. They must understand the study scope, objectives and procedures, including the retrieval instructions and use of the shipping log. The users must be trained and know how to operate the EDLMs.

b. **Critical control points (CCPs):** Prepare a checklist form which identifies every CCP along the route. The form should provide a place for recording the serial number of the accompanying EDLM, the date and time of each CCP, and the signature of the person responsible for completing the checklist entry. The checklist should accompany the shipment to its final destination. It should be used to record the point of entry and exit from each CCP (for example loading a truck or entering a temperature controlled warehouse); this provides the information needed to link the temperature profile to specific events along the route.[12]

c. **Placing data loggers:** In order to capture actual ambient temperature exposure, attach the EDLM to the outside of the shipper, or place in a well-ventilated box immediately next to the product. Do not pack it in with the product itself.

d. **Designate responsible persons:** The study manager must ensure that a responsible person is designated and fully briefed at each origin point and at each receiving site.

e. **Distribution schedule:** Send a detailed distribution schedule to each origin and destination site before the study begins. Alert the responsible person in advance of each shipment in order to avoid delays in retrieving the EDLMs and downloading their data.

f. **Log information:** Create a log to record all key information relating to each shipment and for each EDLM used in the study. It is essential to link the serial number of each logger uniquely to each shipment and to provide responsible persons with key shipping information. This includes: the tracking number; shipment date and time; shipping service level, and destination.

g. **Data collection:** The data collection process begins at the study's point of origin. The EDLMs should be programmed to start recording as soon as the product is removed from controlled temperature storage in preparation for shipment. This will ensure that the device records the temperature of the packing environment as well as the length of time required to pack an entire shipment.

2.4 Data retrieval

The EDLMs must be collected and their data downloaded and emailed to the study manager, and analysed as soon as possible. If there are no facilities for downloading at the destination point, the EDLMs themselves should immediately be returned to the study manager. Observe the following steps:

a. **Data logger retrieval and return:** The responsible person at each receiving site must retrieve the EDLM from the shipment. The device must then be processed as instructed by the study manager and returned to the designated recipient. If required, the means for returning the device – for example a prepaid and addressed envelope – should accompany the EDLM on the outbound journey.

b. **Device calibration:** Ensure that there are valid calibration certificates for all data loggers used in the study. Single-use EDLMs are recommended and these should be supplied complete with the manufacturer's calibration certificate.

c. **Data report and analysis:** Data will be retrieved and analysed to determine temperature statistics for all the loggers used in the study, including:

   - mean temperatures;
   - standard deviations;
   - minimum temperatures;
   - maximum temperatures.

d. **Study errors:** The possibility exists that some data will not be included in the final analysis as a result of routine human error, device failure or other loss. A contingency plan should be defined for such events as:

   - EDLM malfunction;
   - EDLM inadvertently not started/stopped;
   - shipping information is not available for a data logger;
   - loss of EDLM.

[12] Some EDLMs have an event marker button which can be used to "mark" CCPs on the data record. This provides a useful supplement to a checklist, but cannot replace it.

2.5 Understanding temperature exposure: the degree-hour concept

If a passive container, loaded with coolant and TTSPP, is exposed to a given ambient temperature outside the labelled temperature range of the product (typically +2.0°C to +8.0°C), the natural laws of thermal equilibrium dictate that:

- If the ambient temperature is *above* the maximum recommended transport temperature of the product, the container contents will eventually exceed this upper threshold.
- If the ambient temperature is *below* the minimum recommended transport temperature of the product, the container contents will eventually drop below this lower threshold.

Once either of these thresholds is breached, the TTSPP is at risk of damage.

Passive containers are typically qualified by laboratory tests to establish performance at constant high and low ambient temperatures. However, during real-world transport operations, ambient temperature does not remain constant. As noted above, it can fluctuate widely depending upon the time of day, time of year, height changes, hemispheric crossings along the route (in the case of international transport) and the time spent during loading and offloading.

These fluctuations are captured by following the procedures described in sections 2.1 to 2.4 above. By analysing the collected data, the temperature exposure along different routes, or for different instances of a single route, can then be calculated and compared using the *degree–hour* concept. The principle is straightforward. Ambient temperatures are sampled along the different routes at the same time intervals – for example once every 15 minutes. Each data point is then analysed to establish the extent of the exposure above the upper or lower temperature threshold according to the following formula:

$$E = \Sigma\,(T \times t_{dif})$$

Where:

E = temperature exposure in degree–hours;

T = temperature recording interval in hours;

t_{dif} = temperature difference in°C between the threshold temperature and ambient temperature.

Over an entire journey, this formula gives the total degree–hour exposure of the container. This can then be compared with the maximum degree–hour exposure for which the container is qualified.[13] This is the principle adopted for the two methods described in Section 2.6.

2.6 Organizing, analysing and using the data

This section describes how to organize, analyse and use the data. The process of moving from the raw data to a final statistically representative route profile involves a systematic approach to organizing and analysing the collected data and an understanding of simple statistics.

For each shipment, create an Excel® table containing the raw data you have collected – see Table 1. In this simple example, all five journeys are 48 hours long; in reality trip times will vary.

Table 1. Example of an Excel® route profile data table.

EDLM interval 0.25 hrs

Elapsed time	Temperature (°C)				
(hours)	Shipment A	Shipment B	Shipment C	Shipment D	Shipment E
0.00	26.7	22.0	22.0	23.9	18.8
0.25	29.1	24.5	22.3	25.2	19.0
0.50	26.8	27.0	22.7	26.2	19.3
0.75	21.6	30.0	22.9	27.1	20.5
..	..	..	..	..	..
47.25	23.4	25.9	14.4	24.1	21.0
47.50	23.3	26.0	19.4	24.4	20.8
47.75	23.5	26.2	21.1	24.2	20.6
48.00	23.6	26.1	19.0	23.9	20.4
Degree hrs	**912**	**957**	**925**	**1040**	**1042**

Organize and analyse the data as follows:

Step 1: Arrange the data by origin and destination.

Step 2: For each location, create a data table in an Excel® spreadsheet containing the following columns:

- elapsed time in hours based on the chosen EDLM data acquisition interval;
- temperature recorded for each shipment at each of the elapsed time intervals.

Step 3: Calculate the degree–hour value for each column using the Excel® formula:

= *EDLM recording interval * SUM (first data point/last data point)*

Step 4: The column totals indicate the total temperature exposure for five separate shipments in degree–hours above (or below) 0.0°C and allows these exposures to be compared for severity. In the example in Table 1, shipment E has experienced the greatest exposure and shipment A, the least.

Once step 4 has been completed, there are two alternative ways in which the data can be used. *Method A* uses the collected route profile data to create a statistically robust test profile; this can then be used as a basis for testing proposed packaging solutions under laboratory conditions in a temperature-controlled test chamber. *Method B* is an empirical rule-of-thumb approach, for use where the performance of the proposed passive container is already known. For example, this method may be used for prequalified cold boxes and vaccine carriers whose cold-life, cool-life and warm-life at constant ambient temperature have been tested and published.[14]

[13] The degree-hour calculation ignores the effect of solar radiation – a container exposed to the sun may experience a higher effective temperature than the recorded ambient temperature. This radiation effect is also ignored during laboratory testing and is the reason why passive containers should always be kept in the shade.

[14] See for example the cold boxes and vaccine carriers in the WHO PQS catalogue (http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/categorylist.aspx).

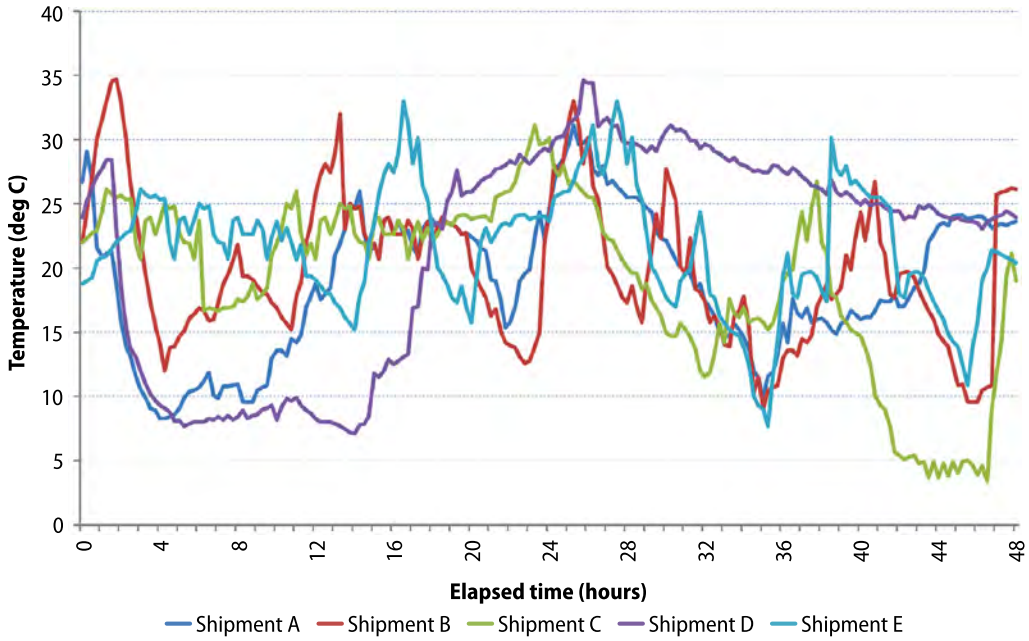
2.6.1 *Method A* for designing and testing packaging solutions

The route profiling data and degree–hour calculations can also be used to derive a test profile; this can then be applied as a basis for conducting the OQ of packaging solutions under laboratory conditions in a temperature-controlled test chamber.

This section describes how to calculate a test profile, using the data from Table 1 as an illustrative example. In practice a larger data set is needed – as previously noted, a sample size of 30 trips on a given route over the course of a year is considered to be statistically valid. If data on fewer than 30 trips are available for analysis, frequent periodic monitoring can be used to verify the results.

Figure 1 shows the data from Table 1 as a graph. These temperature histories demonstrate why viewing a graph without analysing the data can be very misleading.

Figure 1. Example of a temperature profile graph for five shipments.



If we look closely at the five shipment profiles, we can see the following:

- Shipments A and B had similar shipment exposures and similar degree–hour periods (912 and 957).
- Shipment C arrived at its destination around the 40-hour mark but was then put into a refrigerator before the EDLM was switched off at 48 hours. A casual reading of the graph suggests that this shipment had the lowest heat exposure because it spent the lowest and longest period at low ambient temperature. In fact it only had the second-lowest degree–hour exposure (925).
- Shipment D had a very low temperature exposure over the first 15 hours; it was then exposed to very high temperatures from 20 hours onwards. Although this shipment may appear to have been the most exposed it is only the second-worst case (1040 degree hours).
- Shipment E is actually the “worst case” at 1042 degree hours. Even though shipments D and E look very different, they share nearly the same amount of heat under the curve. Graphs can be deceptive.

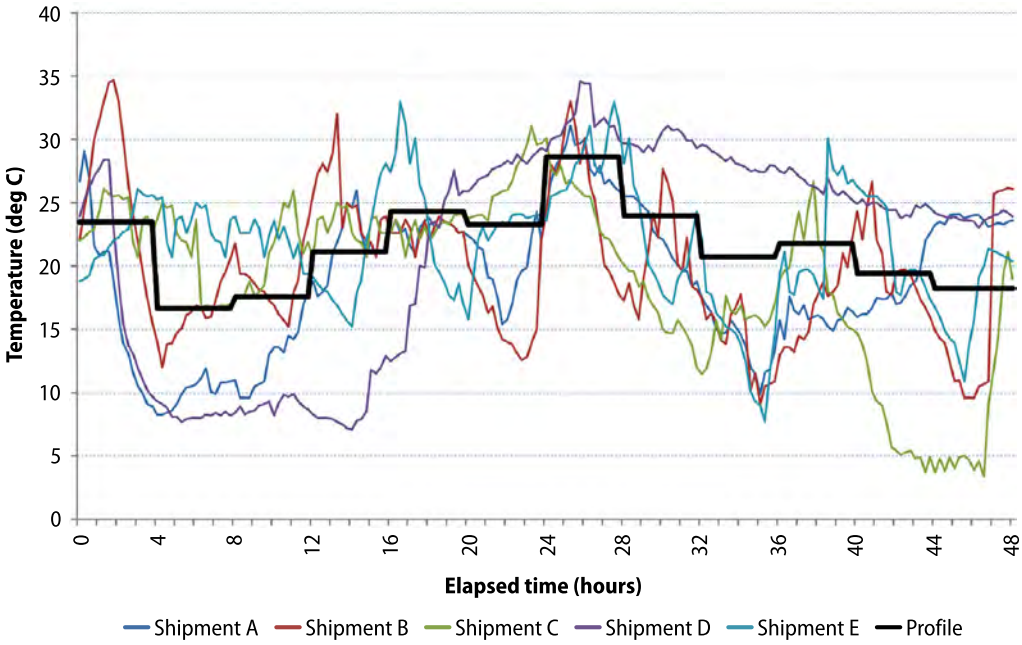
To conduct a laboratory test based on data collected from a set of route profiles, it is necessary to analyse and distil the data into a simplified format which adequately represents the expected temperature exposure of future shipments along the route. This profile can then be used to control the test chamber temperature.

The method illustrated below meets the following objectives:

- The derived profile needs to be in the form of a "step graph". This allows the test chamber thermostat program to be reset at regular intervals.
- The purpose of a step graph is to mimic the typical temperature profile of the route. For example, if the greatest heat exposure occurs at the end of the journey, the step chart must show this. The effect on the package of such variations in the time and extent of exposure cannot be replicated accurately simply by placing the test sample in the test chamber at a constant temperature.
- For practical reasons, the time between temperature changes should be long enough to allow the test chamber to stabilize at each new set point. In practice the intervals should be from one to several hours in duration, depending on the length of the route being simulated.
- The area under the graph should have the same number of degree–hours, or "heat under the curve", as the worst case shipment in the dataset.

Figure 2 shows an example of a test profile derived from a table of EDLM data. The analysis converts the raw data into a simplified step graph with fourhour intervals between steps. In this case, the derived profile which has 1042 degree-hours under the curve – the same as the worst case exposure in the sample of five shipments.

Figure 1. Example of a temperature profile graph for five shipments.



Although the step graph appears to ignore some of the temperature extremes, in reality, so long as the profile follows the exposure timeline AND the worst-case degree-hour condition, it should adequately reflect reality.

2.6.2 *Method B* for passive containers with known performance characteristics

Prequalified passive containers are typically qualified by laboratory testing to establish performance at constant high and low ambient temperatures; for example, WHO prequalified containers are tested at +43.0°C and –20.0°C and these performance figures are published.[15]

Once the ambient temperature profile of a transport route is known, these published figures can be used to estimate the *actual* performance of a given container over that specific route – this will nearly always be longer or shorter than the published figure, because ambient temperatures fluctuate.

All passive containers have a finite cold life, cool life or warm life "budget". In a real-life situation, with constantly changing ambient temperatures, the way in which this cool life budget is "spent" depends on the actual temperatures that the container experiences:[16]

- When the ambient temperature is on average above +43.0°C the cool-life budget will be "spent" more quickly than in the laboratory test and cool life will be shorter.
- When ambient temperature is on average less than +43.0°C the coollife budget will be "spent" more slowly and cool life will be longer.
- If the ambient temperature remains between 0.0°C and +20.0°C the container will keep vaccine below the cool-life threshold permanently.
- If the ambient temperature remains between 0.0°C and +8.0°C the container will keep vaccine below the cold-life threshold permanently.
- If the ambient temperature is on average below 0.0°C, the contents of the container will cool down and eventually drop below 0.0°C.

If the ambient temperature fluctuations are known (the route profile) the following formula can be used to assess a container's actual performance over that route.

$$E = \Sigma\ (h \times t_{dif})$$

Where:

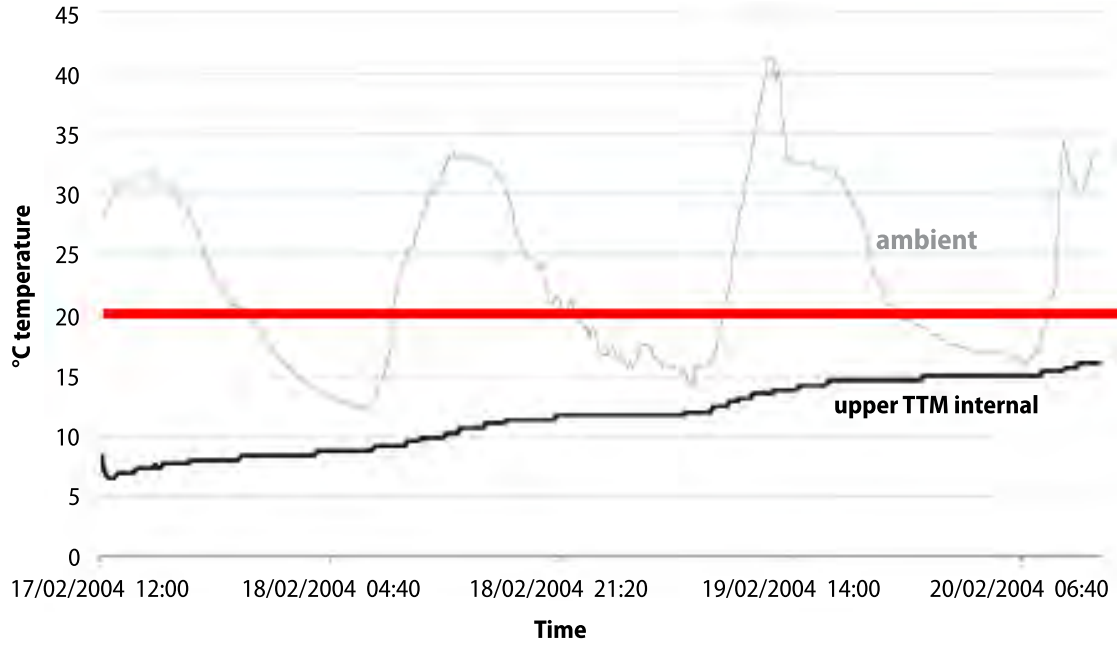
E = total temperature exposure above the threshold temperature, in degree-hours;

T = time increment above the threshold temperature, in hours;

t_{dif} = temperature difference in°C between the threshold temperature and ambient temperature for each increment.

Figure 3 shows the temperature profiles inside and outside the container for a monitored shipment in Myanmar, using cool water-packs. The upper line on the graph shows the ambient temperature along the route and the lower line shows the temperature inside the cold box. There were four periods during which the ambient temperature was higher than the +20°C temperature threshold line. Only during these periods was the temperature inside the cold box being forced above the threshold temperature. In this example, the contents never reached +20°C, even though the journey lasted nearly 67 hours. The laboratory-tested cool life for the Dometic RCW25 model used for the test is 34.4 hours, only about half that achieved in practice over this route.

Figure 3. Temperature profile in Myanmar.



Adapted from: Kartoglu et al. (2009).
Upper TTM internal is the temperature profile in the load.
TTM, time-temperature monitoring device (user-programmable temperature logger).

This example illustrates how route profiling can be used to provide evidence that it is safe to use a specific container for journeys that are longer than the published performance figures. Note that, in a very hot climate, the maximum allowable journey time may be shorter than the published performance figures suggest.

Annex 1 gives worked examples of the use of this method. The route profile data is used to establish whether the degree-hour exposure of the worst-case route profile exceeds the laboratory-tested performance of a proposed passive container, also calculated in degree-hours. This is a two-step operation and there are two cases – a *warm climate* situation where the ambient temperature is consistently above the maximum recommended temperature for transport of the TTSPP and a *cold climate* situation where the ambient temperature is consistently below the minimum recommended temperature for transport of the TTSPP.

Note: Method B is not suitable for use in cases where the ambient temperature fluctuates above and below 0.0°C. In addition, because it is based on a simple empirical calculation, it is strongly recommended that this method should only be used for in-country transport operations.

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ANNEX 1.1

SUPPLEMENT 14

METHOD B EXAMPLES

This Annex describes the use of Method B outlined in section 2.6.2 in more detail.

A1.1 Using the data

Systematically collected route profile data can be used to establish whether a specific prequalified container and coolant combination is suitable for a specific route. There are two situations – a *warm climate case* where the ambient temperature along the route is above 0.0°C and a *cold climate case* where the ambient temperature over the route is generally below 0.0°C.

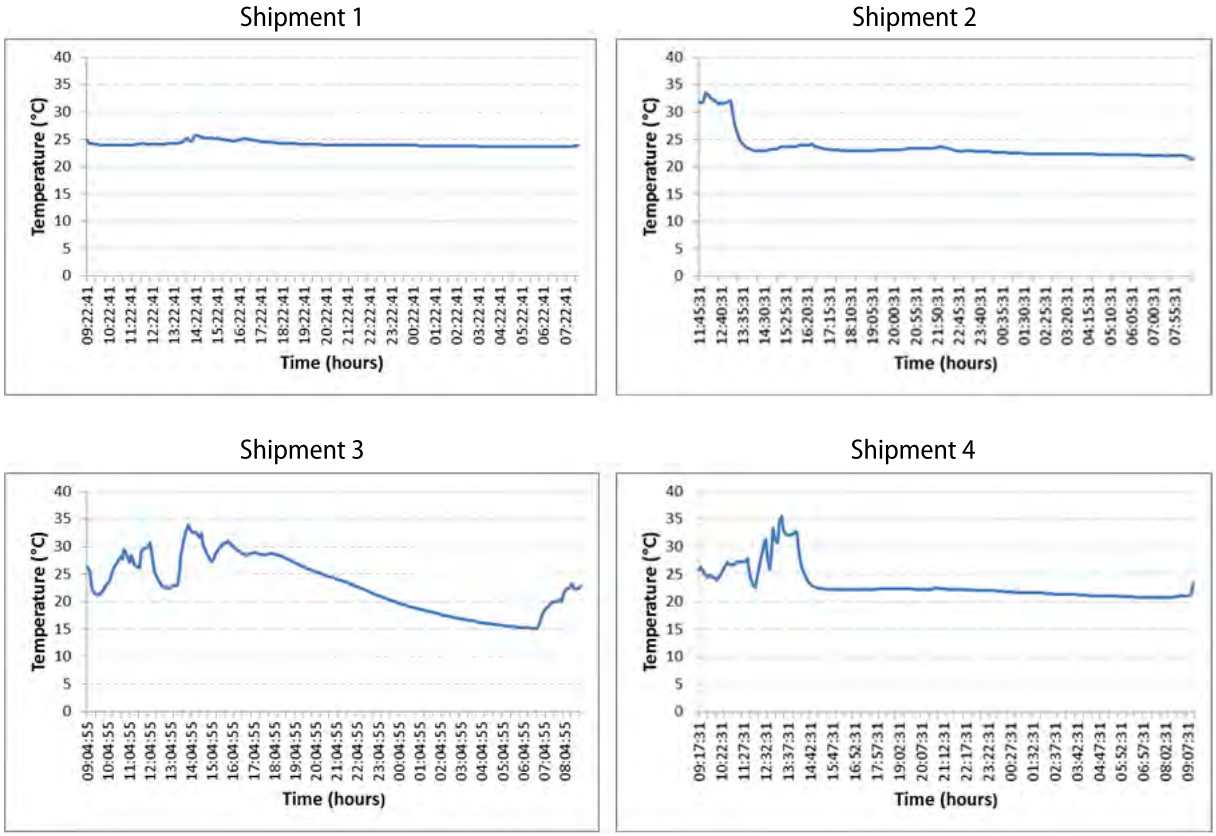
Note: The method described below is not suitable where the ambient temperature profile fluctuates more or less equally above and below 0.0°C AND where conditioned ice-packs or cool water-packs are used to transport freeze-sensitive TTSPPs. Under these circumstances there is a risk that the product may freeze. Such routes should be validated using test shipments where both ambient and load temperatures are monitored.

Section A1.2 describes the calculation method for the warm climate case and section 1.3 describes the method for cold climates.

A1.2 The warm climate case

Figure A1.1 shows four ambient temperature route profiles recorded in a central Asian country. All four examples are for journeys of around 24 hours.

Figure A1.1. Route profile examples.



For each shipment, create an Excel® table containing the raw data you have collected – see Table A1.1.

A1.2.1 *Step 1:* organize and analyse the route profile data

Organize and analyse the data as follows:

a. Arrange the data sets by origin and destination.

b. For each location, create a data table in an Excel® spreadsheet containing the following columns:

- Elapsed time in hours based on the selected logger recording interval.
- Temperature recorded for each shipment after each of the elapsed time intervals.

c. Select the threshold temperature. In this example we will use +20°C.

d. Calculate the total degree-hour value for each column using the Excel® formula:

Warm climate case:

*E = SUMIF (first data point/last data point,">threshold temperature\"", first data point : last data point) * logger interval in hours)*

The column totals indicate the total temperature exposure for the separate shipments in degree-hours above the chosen threshold temperature and allows these exposures to be compared for severity.

e. Finally, calculate the total journey time for each shipment.

Once the last step has been completed, the data can be used to check the suitability of a proposed prequalified passive container/coolant-pack combination as described in the next section. Table A1.1 shows part of the data for the four journeys in Figure A1.1.

Table A1.1 Example of an Excel® route profile data table

Recording interval: **0.25 hours**
Threshold temperature: **+20°C**

Elapsed time	Temperature (°C)			
(hours)	Shipment 1	Shipment 2	Shipment 3	Shipment 4
0.00	24.8	31.7	26.2	25.7
0.25	24.2	33.5	22.1	25.1
0.50	24.1	32.5	21.2	24.8
0.75	24.0	31.7	22.1	24.2
1.00	23.9	31.5	23.5	24.7
..	..	..	..	..
23.75			22.8	21.1
24.00				21.8
Degree-hours above 20°C	**547**	**493**	**414**	**557**
Total journey time (hours)	**22.50**	**21.00**	**23.75**	**24.00**

In this example, Shipment 4 received the greatest degree-hour exposure. Shipment 3 received significantly the least, even though the peak temperature rose to nearly 35°C; the reason for this is that the ambient temperature dropped below the 20°C threshold for around eight hours. All of the other three profiles remained above the threshold temperature throughout.

A1.2.2 *Step 2:* assess container suitability

We can now assess whether a given cold box or vaccine carrier is suitable for the four routes, as follows:

a. Vaccine carrier type A has a rated cool life of 12 hours at +43°C. This can be expressed in another way as a cool life "budget" of 12 × 43 = 516 degree-hours.

b. Five hundred and sixteen degree-hours is less than the degree-hour exposure for shipments 1 and 4, but greater than the exposure for shipment 2 and 3. On this basis, the type A container could therefore be used for these last two routes, even though both journey times are nearly twice as long as the rated cool life of the type A container.

A1.3 The cold climate case

The procedure is similar to the warm climate case except that the Excel® formula is slightly different.

A1.3.1 *Step 1:* organize and analyse the route profile data

Organize and analyse the data as follows:

a. Arrange the data sets by origin and destination.

b. For each location, create a data table in an Excel® spreadsheet containing the following columns:

- Elapsed time in hours based on the selected logger recording interval.
- Temperature recorded for each shipment at each of the elapsed time intervals.

c. Calculate the total degree-hour value for each column using the Excel® formula:

*E = SUMIF (first data point/last data point,"<threshold temperature\"", first data point : last data point) * logger interval in hours)*

The column totals indicate the total temperature exposure for the separate shipments in degree-hours below the chosen threshold temperature and allow these exposures to be compared for severity.

d Finally, calculate the total journey time for each shipment.

Table A1.2 shows some hypothetical data. Once the last step has been completed, the data can be used to check the suitability of a particular prequalified passive container /warm-pack combination as described in the next section.

Table A1.2 Hypothetical data for a cold climate profile.

Recording interval: **0.25 hours**
Threshold temperature: **0°C**

Elapsed time	Temperature (°C)			
(hours)	Shipment 1	Shipment 2	Shipment 3	Shipment 4
0.00	15.00	16.5	15.5	13.5
..	..	..	..	..
23.75			-15.0	-12.5
24.00				-12.8
Degree-hours below 0°C	**-254**	**-338**	**-413**	**-304**
Total journey time (hours)	**22.50**	**21.00**	**23.75**	**24.00**

In this example, shipment 1 has the lowest exposure to sub-zero temperatures and shipment 3 has the highest.

A1.3.2 *Step 2:* assess container suitability

We can now check whether a proposed passive container has a long enough warm life to be suitable for the routes in the data set:

a. Vaccine carrier type A has a rated warm life of 21.6 hours at –20°C. This can be expressed in another way as a warm life "budget" of 21.6 × –20 = –432 degree-hours.

The budget of –432 degree-hours is less than the degree-hour exposure for all four shipments. On this basis, the type A container could safely be used on any of the routes.

REVISION HISTORY

Date	Change summary	Reason for change	Approved

ANNEX 2.

SUPPLEMENT 13

QUALIFICATION OF SHIPPING CONTAINERS

TECHNICAL SUPPLEMENT TO WHO TECHNICAL REPORT SERIES, NO. 961, 2011.

Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products.

May 2015

CONTENTS

ABBREVIATIONS

ASTM	American Society for Testing and Materials
DQ	design qualification
EDLM	electronic data logging monitor
ISPE	International Society for Pharmaceutical Engineering
ISTA	International Safe Transit Association
OQ	operational qualification
PDA	Parenteral Drug Association
PQ	performance qualification
SOP	standard operating procedure
TTSPP	time- and temperature-sensitive pharmaceutical product
URS	user requirement specification

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GLOSSARY

Active systems

Externally powered or on-board powered systems using electricity or another 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 ° Celsius, phasing from one state of matter to another (i.e. liquid to solid) at a pre-formulated temperature. Such materials typically comprise 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.

Associated components

Articles of packaging that are typically intended to deliver the dosage form to the patient but are not stored in contact with the dosage form for its entire shelf life. These components are packaged separately in the market package and are either attached to the container upon opening or used only when a dose is to be administered. Examples are measuring spoons, dosing cups, and measuring syringes.

Cryogenic dry/vapour shipper

A temperature-controlled insulated packaging container or system compatible with liquefied gases such as nitrogen used for maintaining extremely low temperatures during shipping. A porous medium internal to the shipping container absorbs and contains all the free flowing liquid and does not allow it to come into contact with the product – a process known as “charging”. A fully charged and undamaged dry/vapour shipper containing nitrogen can maintain –196°C for up to 10 days, depending on the unit size.

Design qualification (DQ)

The process of obtaining and documenting evidence that the premises, equipment and supporting systems and processes have been designed in accordance with the requirements for good manufacturing practices (GMP).[1]

Dunnage

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

Electronic data logging monitor (EDLM)

A small portable device that measures and stores temperature at predetermined 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 monitoring and event logger system (EDLM)

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*.

Installation qualification (IQ)

The process of obtaining and documenting evidence that the premises, equipment and supporting systems have been provided and installed in compliance with their design specifications.

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*.

Maximum payload

The amount of product intended to be shipped with the most amount of thermal mass.

Minimum payload

The amount of product intended to be shipped with the least amount of thermal mass.

Operational qualification (OQ)

The process of obtaining and documenting evidence, under controlled conditions, that the premises, equipment and supporting systems operate in accordance with their design specifications.

[1] WHO Technical Report Series, No. 961, 2011. Annex 3: WHO good manufacturing practices for pharmaceutical products: main principles.

Packout

An assembled package that includes the product to be shipped (alternatively, simulated product in its primary packaging form used for its commercial presentation, the insulated shipper or container, any and all necessary auxiliary and/or associated components and ancillary packaging components such as temperature stabilizing medium, secondary packaging, partitions, bubble wrap, data loggers or other temperature monitoring units, and dunnage.

Passive systems

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

Performance qualification (PQ)

The process of obtaining and documenting evidence that the premises, equipment and supporting systems, as connected together, will consistently perform in accordance with the approved process method and specifications.

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.[2]

Prequalified shipping container system

A packaging container or packaging system in which a DQ and OQ have already been established and documented by the manufacturer and the user has acquired sufficient documentation to meet their user requirement specification (URS).

Qualification protocol

A written and approved plan detailing how a qualification will be conducted including test parameters, product characteristics, equipment and acceptance criteria.

Qualification

Action of proving that any premises, equipment and supporting systems work correctly and actually lead to the expected results. The meaning of the word *validation* is sometimes extended to incorporate the concept of qualification.

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.

Seasonal packaging solution (also called a dedicated packaging solution)

A packed shipping container system, whose effective performance in different seasons requires more than one packing configuration. These configurations depend on seasonal variants such as summer and winter or hot and cold season exposure.

Secondary pack or carton or market package

The package presentation intended for the end-user (e.g. bottle + cap liner + dose cap + leaflets + carton) but not including packaging used solely for transport purposes (e.g. *Tertiary carton or Insulated shipper*). The secondary pack may contain multiple units of product.

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, and 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 predefined limits.

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

Time and temperature-sensitive pharmaceutical product (TTSPP)

Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

Transport temperature profile

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

Universal packaging solution

A shipping container whose proper performance does not require more than one packing configuration regardless of seasonal variants such as summer and winter or hot and cold exposure.

User requirement specification (URS)

The attributes assigned by the user in advance of a qualification test to establish minimum performance limits. Sometimes referred to as a *functional requirements document.*

Validation

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

[3] Parenteral Drug Association (PDA) Technical Report No. 39: Guidance for temperature controlled medicinal products: Maintaining the quality of temperature-sensitive medicinal products through the transportation environment. Bethesda (MD): PDA; 2007.

1. INTRODUCTION

This technical supplement has been written to amplify the recommendations given in section 6.8.3 and 6.8.4 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]

Understanding the environment through which a TTSPP must travel is essential for successful logistics operations, for package design, and for maintaining the quality of the pharmaceutical product during external distribution. The best way to understand the temperature hazards that may occur during external distribution is to collect actual temperature data from representative parts of the supply chain. This process dispels assumptions, and can reveal weaknesses, risks and trends within the transport system. This document describes a method for profiling transport routes which is simple to understand and to execute; it is based on an approach called the "heat under the curve" method. Other techniques can also be used, but these tend to be more complex.

Temperature information gathered from a route profiling exercise can be used to develop representative ambient temperature profiles for specific lanes, modes and durations of transport. Route profiling is a prerequisite for carrying out a statistically representative operational qualification (OQ) or performance qualification (PQ) exercise involving shipping containers and refrigerated vehicles.

This supplement should be read in conjunction with the companion Technical Supplements: *Qualification of shipping containers and Qualification of temperature-controlled road vehicles*.

What is qualification?

In the context of this series of Technical Supplements, *qualification* is an inspection and testing process used to establish that a piece of equipment or a physical installation is fit for purpose in the operational context within which it will be used. There are typically three stages in the process. Each stage must be fully completed before the next one begins.

Design qualification (stage 1 for equipment): Establish by laboratory testing under tightly controlled conditions that a specific item of equipment performs in accordance with the user requirements specification (URS). This is *design qualification*. While design qualification demonstrates compliance with the URS and associated test protocols; it does not prove that the equipment will be suitable in a specific operating environment because the URS and the test procedures are unlikely to reflect the full range of operating conditions.

Installation qualification (stage 1 for installations): Establish by documented inspection and testing that an installation[5] that has been assembled in a specific location is fully in accordance with the URS and installation drawings.

Operational qualification (stage 2): Establish by further documented testing under controlled conditions that this equipment or installation is likely to perform as intended in the operating environment in which it will be used.

Performance qualification (stage 3): Carry out a final stage of documented testing to establish with a high degree of assurance that the equipment or installation, together with all associated systems, does indeed perform as intended under routine operating conditions.

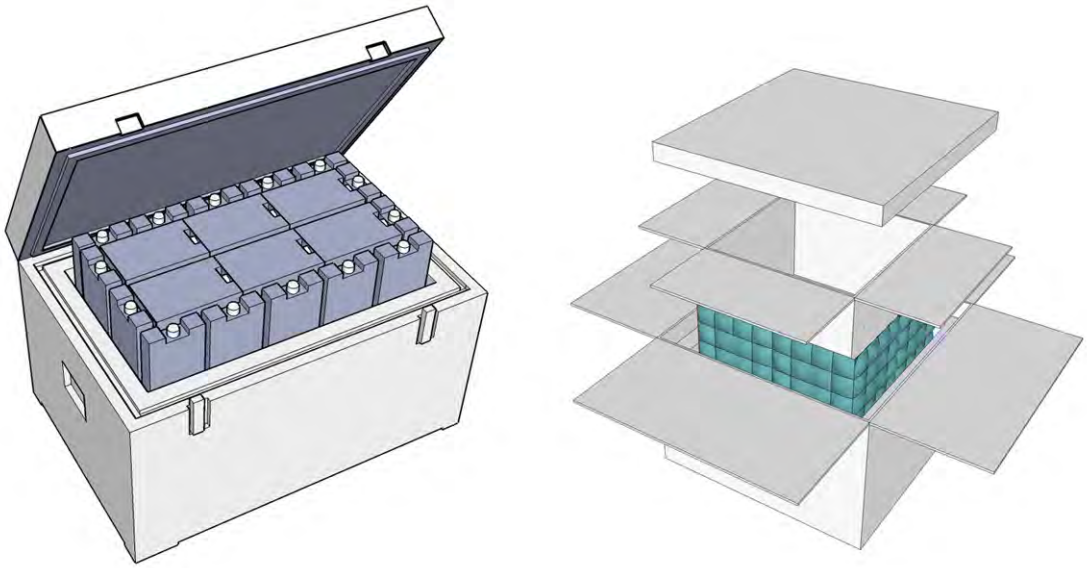
[4] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf
[5] The installation will typically incorporate components that have been design qualified.

1.1 Requirements

Transport operators and end-users need to be sure that TTSPPs are delivered in container systems that are capable of maintaining a predefined internal temperature range during transport, can minimize product degradation as a result of temperature-sensitivity, and can meet the product stability profile requirements stated by the pharmaceutical manufacturer. Regulatory authorities and other interested parties require documented evidence that such assurance and compliance can be demonstrated and maintained.

Every shipping container system must be fully qualified to show that it is "fit for purpose" and capable of maintaining a TTSPP within the temperature range needed to meet the product manufacturer's stability profile, under the anticipated transport conditions. Qualification must also demonstrate that the system can sustain handling and transport while protecting the physical integrity of the product. These multiple challenges are described in the user requirement specification (URS). Figure 1 illustrates the two types of passive container covered by this document. Active containers come in many types and are not illustrated.

Figure 1 Generic passive containers with coolant packs (WHO).



Reusable container

Disposable insulated carton

As noted above, qualification consists of three sequential testing stages: DQ, OQ, and PQ. If the container manufacturer can demonstrate that the product has already passed an appropriate conformity assessment or that it has already been independently prequalified by a standard-setting organization such as the World Health Organization (WHO),[6] the DQ stage is not required. In both these cases DQ will have formed part of a pre-purchase assessment process. If the system manufacturer is additionally able to supply a satisfactory OQ report, which meets the end-user's needs, the OQ stage may also be dispensed with.

1.2 Objectives

The objective of this technical supplement is to provide advice on how to ensure that shipping container systems meet the performance parameters defined in the URS with a high degree of certainty and repeatability.

1.3 Target readership

This document is intended for use by anybody who is responsible for maintaining quality during the process of assessing, procuring and using TTSPP shipping container systems.

These parties need to appreciate the importance of temperature stability for pharmaceutical products, have a sound working knowledge of applicable logistics and transportation methods within their organizations, and understand the basic concepts of packaging thermodynamics.

Those who are responsible for conducting qualification testing must be capable of operating the equipment necessary to complete the tests and be familiar with, and follow, good laboratory documentation practices.

[6] See: http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/categorypage.aspx?id_cat=18.

2. GUIDANCE

It is most likely that the users of this document will be assessing the performance of an existing "prequalified" packaging system. Section 2.1 gives a brief introduction to all three types of qualification – DQ, OQ and PQ. The remainder of the guidance section focuses principally on PQ. However, if a DQ and OQ have not been completed, it is the responsibility of the user to complete these two stages before proceeding to the PQ. In all cases, a URS must be written and approved before testing takes place. Any deviations from the test protocols must be documented as an "exceptional condition".

2.1 The three stages of qualification

Before any qualification stage is begun, carry out a risk assessment to identify the environmental conditions and the distribution lanes through which the proposed container will travel. This process helps ensure that the proposed qualification procedure will match the intended use. Consider the anticipated scenarios when deciding on the qualification temperature ranges.

Full details of the packaging assembly must be defined, tested and documented for each of the three stages of the qualification process. These details include the thermal conditioning regime for system components and the products being transported, product loading arrangements and the location of temperature monitor(s). Test dates should also be recorded in all qualification reports.

It is strongly recommended that both minimum and maximum product loads are tested at each stage. The test loads should be chosen to represent the products which will be transported. In most cases the lowest thermal mass products are the ones most susceptible to temperature change. Accordingly, the minimum load in a test should represent a shipment of a minimum quantity of the lowest thermal mass product and the maximum load should represent a full payload of this same product.

Qualification must also take account of the transport route(s) and modes of transport and the anticipated ambient temperature profile over the duration of transport. Transport time is measured from the time the completed package is closed and sealed at the point of departure, until the package is opened at the point of arrival in the recipient's temperature-controlled store.

2.1.1 Design qualification

All new shipping container systems must successfully meet the predefined acceptance criteria set out in an approved DQ protocol or project scope document. In the case of a system that is already prequalified, it will only be necessary to repeat the DQ stage if the system specifications do not appear fully to meet the requirements of the end-user's original URS. This URS should clearly define product load specifications, ambient temperature profiles, shipping duration, and allowable product temperature range. Other performance characteristics may also need to be included in the document.

DQ takes place under laboratory-controlled conditions against an approved DQ protocol. This protocol defines the tests needed to evaluate basic design requirements, constraints and suitability for use. Any deviations from the protocol must be documented as an "exception condition". At a minimum, the following list of packaging configurations should be tested unless otherwise specified:

a. one heat profile, maximum product load;

b. one heat profile, minimum product load;

c. one cold profile, maximum product load;[7]

d. one cold profile, minimum product load.

The purpose of these tests is to collect enough evidence to establish that the container design concept is sound and to justify moving on to the OQ stage. OQ should not take place until the DQ stage is satisfactorily completed including simulated transport stress tests (vibration and drop), which are a required part of DQ.

2.1.2 Operational qualification

As with the DQ stage, an OQ may not be required when a prequalified shipping system is used. In such cases, an OQ report can often be provided by the container system supplier, either free of charge, or for a fee. However, if a prequalified shipping system OQ report is relied upon, no substitutions or modifications to the design or packaging can be made and the performance of the system as set out in the report must demonstrably meet or exceed all the specifications in the end-user's URS.

If substitutions or modifications to the design or packaging are made an OQ must be carried out; there may also be other reasons to justify the need for an OQ. OQ is carried out under laboratory-controlled conditions and the OQ protocol must clearly define the packout arrangements and the acceptance criteria for the shipping system(s) to be qualified. As a minimum, the protocol must define the following test criteria as derived from the initial risk assessment exercise: transport duration, acceptable temperature range, payload details, ambient temperature profiles, location of temperature monitoring devices, location of refrigerant, and refrigerant conditioning specifications.

[7] Products that can safely be shipped frozen do not need cold profile testing.

Other test criteria may also need to be included – for example transport and stress tests (vibration and drop) – and the OQ protocol must be approved by all stakeholders before qualification testing takes place. To demonstrate repeatable performance the OQ tests must be carried out in triplicate and must successfully meet the acceptance criteria in every one of these tests.

When the OQ is complete, prepare a final report; this should document the test performance and compare the results with the acceptance criteria set out in the OQ protocol.

2.1.3 Performance qualification

The final stage of qualification – the focus of this document – is the PQ; this stage is mandatory in all cases, except where every shipment on every route is monitored. PQ is conducted as a field test in the real operating environment. A PQ protocol must be developed to document the process and define the acceptance criteria; these criteria should be similar to those defined in the DQ and OQ protocols. The PQ protocol should be representative of existing shipping operations and must include:

- the number of “ship-to” locations;
- the number of “ship-from” locations;
- the number of shipments to be tested;
- the time of year the shipments are to occur.

As with the OQ, PQ tests must be performed three times, and must successfully meet the acceptance criteria in every instance, in order to demonstrate repeatable performance. Once the PQ is complete, prepare a final report which documents the test results and compares them with the PQ acceptance criteria.

2.1.4 Re-qualification of reusable container systems

Reusable shipping container systems, with and without interchangeable parts, should periodically be re-qualified to ensure that the thermal performance has not been adversely affected as a result of age, change in chemical properties, physical damage, off-gasing, evaporation of temperature stabilizers, or other potential performance loss. Generally, this re-qualification process is user-defined; typically it is done on annually, on the basis of a risk assessment, or when there is some significant change in transport operations.

2.2 Associated materials and equipment

Below is a list of the minimum equipment required to perform a DQ, OQ or PQ qualification.

2.2.1 Test equipment for design and operational qualifications

This DQ and OQ list is primarily for information purposes. It can be used to check that the correct equipment has been used for testing prequalified containers that are put forward for PQ.

- Thermal test chamber(s) of sufficient size to accommodate the package(s) being tested. The chamber(s) must be capable of simulating ambient temperatures within the required ambient temperature profile ranges and able to condition components; both within a tolerance of ±3°C.
- A multi-channel temperature data logger with a sufficient quantity of thermocouples capable of producing a permanent record of temperature and elapsed time with an acceptable operating tolerance of ±0.5°C for temperatures > –18°C and ±0.8°C for temperatures ≤ –18°C;

or a portable electronic temperature data logging monitor (EDLM) capable of producing a permanent record of temperature and elapsed time with an acceptable operating tolerance of ±0.5°C, over a temperature range approximately between –20°C and +50°C.[8]

- Calibration bath – for thermocouple verification.
- Weighing scale with an accuracy of ±5% of the gross container weight.
- Packaging materials.

Other equipment may also be needed for testing package robustness, resistance to vibration and the like.

2.2.2 Test equipment for performance qualification

- Portable electronic temperature data logging monitors (EDLMs) capable of producing a permanent record of temperature and time elapsed with an acceptable operating tolerance of ±0.5°C, over a temperature range approximately between –20°C and +50°C.
- Complete packout configurations.

Wherever possible, use the same equipment for the PQ tests as is used for the OQ tests.

[8] The accuracy of EDLMs that use thermistors as a means of determining temperature is less at the outer limits of their operating range. It is acceptable to have wider tolerances for temperatures outside this range: e.g. ±0.8°C for temperatures ≤ –18°C, or ±2°C for temperatures below –40°C (dry ice shipments).

2.3 The performance qualification test protocol

A PQ protocol details the field testing procedures needed to verify the results of an OQ in the intended distribution environment. A comprehensive protocol should include the following sections:

2.3.1 Protocol title

Describe the project in the main title of the form. In the subtitle identify the test container, test product, temperature range, duration and any other unique information. Make it clear that this is a PQ protocol.

2.3.2 Protocol approvals

List the project stakeholders. Include company, position, space for signatures, and dates.

2.3.3 Introduction

Briefly describe the packaging configuration and the acceptance requirements of the test system. Define all abbreviations used in the protocol and provide a glossary of technical terms if needed.

2.3.4 Purpose

The purpose statements should begin with the words: “the purpose of this xxx protocol is…” followed by a brief description of why the protocol was written and what information the document contains. Include details of the test container, product loads, coolants, temperature range, and duration.

2.3.5 Scope

Describe the qualification strategy, how the testing will be performed and how the data will be represented. This should include full details of the test container, minimum and maximum product load specifications, and the number of tests to be performed against which ambient profiles.

2.3.6 Acceptance criteria

Define the required product temperature range and minimum required transport duration. Any applicable product temperature excursions and other design priorities or constraints must also be defined.

2.3.7 Responsibilities

List the personnel or groups responsible for protocol writing, execution, testing, sampling, report writing, and approval. If a contract testing facility is to be used, identify the facility in this section.

2.3.8 Test procedure

Describe the necessary step-by-step procedures used to perform the PQ:

a. unique test number identification;

b. equipment and materials – list all items used;

c. list all test material preparation or conditioning requirements;

d. identify test equipment – include applicable calibration certificates;

e. describe the packout details;

f. describe temperature monitoring or thermocouple probe placement;

g. include isometric drawings, graphics or photographs as needed to describe packouts, location of EDLMs and the like;

h. define the frequency of data recording;

i. include shipping and receiving documents, when applicable;

j. provide a signature log for all personnel who perform, verify, or review the protocol;

k. record packout start-time, weight, and end-time on a worksheet;

l. record monitor location, test date, ship-to and ship-from locations and end-time.

2.3.9 Data analysis

Define how the data generated from the testing will be interpreted.
This includes:

- Equilibration duration – the time required by the shipping container system to reach the required temperature before shipment.
- Temperature of the product during testing gathered from the EDLMs.
- Total time during which product remains within the required temperature range (in hours and minutes)

Record all temperature data in degrees Celsius.

2.4 The performance qualification test

A PQ uses actual field shipments to verify that the DQ and OQ processes are representative and can effectively and consistently provide reproducible results. Carrying out a proper PQ can take from several weeks up to several months. This period depends on the quality of the test protocol design, the test parameters, and the number of tests performed.

At least three tests per shipping container are required for both the minimum and maximum product payload. At a minimum, each series of tests should be conducted during the warmest and coolest part of the year.

Additional tests can be conducted at other times during the year, or whenever new containers are being considered for adoption. If the test container is to be used on multiple routes, determine and choose the worst-case shipping lane and transport method; this will expose the container system to maximum stress in terms of temperature and duration.

Table 1 gives an example of a test schedule with one container type, two packaging configurations and two temperature profiles; this combination requires a minimum of 12 tests to be performed. The number of tests needed increases significantly with each added variable. It is therefore wise to minimize the number of container sizes and the variability in packing configurations.

Table 1 Example of a test schedule.

Ambient profile	Load configuration	Test number
Hot profile	Minimum product load	Test 1-1
		Test 1-2
		Test 1-3
	Maximum product load	Test 2-1
		Test 2-2
		Test 2-3
Cold profile	Minimum product load	Test 1-1
		Test 1-2
		Test 1-3
	Maximum product load	Test 2-1
		Test 2-2
		Test 2-3

The principal steps in the PQ testing process are as follows:

a. For each season (summer and winter or hot season and cold season), identify representative "ship-from" locations.[9] For each of these departure points identify the "ship-to" location that provides the most challenging shipping route. Use these locations for the PQ study. Typically, the chosen routes will include those combining the longest duration with the most extreme temperatures, both hot and cold.

b. Once the worst-case shipping lanes are defined, list these in the PQ protocol for future reference, together with the justification for their selection.

c. Wherever possible, use actual product as the payload for PQ testing. Another option is to use expired samples of the real product because this eliminates the risk of damage to potent, in-date TTSPPs. If real or expired product is not available, use a suitable and representative payload substitute. The substitute payload should have a similar thermal mass, freezing point and packaging as the actual payload.[10]

d. Before conducting each test, condition the payload at its standard storage temperature for the minimum time needed to achieve a uniform temperature throughout the payload (e.g. +2°C to +8°C for 24 hours). The conditioning equipment being used should be able to maintain the temperature set point within ±3°C and the conditioning process should be monitored and documented to ensure compliance.

e. At the same time condition the temperature stabilizing medium in accordance with an approved SOP or according to the container manufacturer's instructions. The conditioning equipment being used should be able to maintain the temperature set point within ±3°C.

f. Use portable EDLMs to acquire the temperature data during the test. The logger(s) should be calibrated (National Institute of Standards and Technology (NIST) traceable) and have a valid calibration certificate; this certificate should be included in the final report. The resolution of the logger(s) should be 0.1°C or better. The accuracy should be ±0.5°C, over a temperature range approximately between –20°C and +50°C.[11]

g. Programme the EDLMs so that the maximum temperature-recording interval is no greater than 30 minutes (5 or 10 minutes is better). The logger's sensor response time should be less than the chosen recording interval and the device should have sufficient memory to hold all recorded data for the entire shipment at the chosen recording interval.

h. Precondition the EDLMs at the standard storage temperature (see d. above). An alternative approach is to activate the EDLM's "delayed start" function so that the device does not begin recording until it has cooled down to the temperature of the payload.

i. Use a minimum of one interior payload EDLM and one external ambient EDLM for each test. The payload EDLM(s) should be positioned to capture temperature variation or temperature stratification within the payload space. Multiple loggers may be needed to achieve this.

[9] See Technical Supplement: Transport route profiling qualification.
[10] This could be a low-value "placebo" product chosen to reduce the risk of financial loss.
[11] See footnote 10 above.

j. Place the interior EDLMs in direct contact with the payload whenever possible. If a single logger is used it should be located in the spot most susceptible to failure; in many cases this is likely to be a top corner of the payload. If OQ test data are available, consult the OQ report to determine the most susceptible locations. The exterior logger should be positioned so that the logger's sensor has reasonable, unobstructed access to the ambient air while taking into account the need to protect the device from damage during shipment. This can be used to correlate air to product temperature data by referring back to the OQ testing from the PQ results.

k. Pack each shipping container in accordance with the manufacturer's instructions, or in the same manner that the product was packed in the OQ (if applicable).

l. After proper conditioning, place the temperature stabilizing medium and the test payload into the payload space. Secure the interior EDLM(s) in the predetermined location(s). Tape the devices in position so that they cannot shift during transit. If required, insert non-insulating dunnage before closing the container to prevent the payload from shifting in transit. Attach and secure the external ambient logger in the predetermined location. The readings from this device enable the analyst to identify how the ambient temperature profile relates to any temperature excursions that may occur in the payload.

m. Seal the container with packaging tape (or tamper-evident tape) and ship along the predetermined route.

n. In addition to monitoring thermal performance, the PQ should include a visual inspection of the physical condition of the container at the destination. The container should show no sign of damage or deterioration at the point of arrival. Physical damage may adversely affect thermal performance, product handling, storage or safety.

n. A PQ worksheet should be completed for each individual container system. This should document the preconditioned refrigerant and product loads, the time at which the container system was fully packed and sealed, the serial number of the EDLM(s), the package weight (net and gross), and the shipment tracking number.

p. Provide clear instructions to the individual(s) responsible for receiving the container. These instructions should fully describe any post-test analyses and give instructions on downloading and distributing the temperature data obtained from the EDLM(s).

q. When the PQ shipping studies are complete, analyse the temperature data and other information collected and determine whether the acceptance criteria, defined by the PQ protocol, have been met.

r. Compile a final report which details the findings of the study. Refer to section 2.5 for information on what to include in this report.

It is recommended that a PQ study should be repeated on a risk-based frequency cycle. In addition, carry out periodic monitoring to determine the need for additional PQ. This helps give assurance that there have been no changes to the distribution lanes used for the transport of the temperature-sensitive products. Any such changes may impact the temperature performance of the load.

Re-qualification should be considered whenever there are changes to components, shipping routes or shipping duration.

2.5 The performance qualification report

The PQ report should summarize the test data and performance characteristics established during qualification testing and provide conclusions based upon these data. The report should include a copy of the test protocol with signature log, complete equipment list, and material specifications. In addition, it should include test graphs, complete test worksheets, all testing data, equipment calibration certificates, and any applicable deviation reports.

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Parenteral Drug Association (PDA) Technical Report No. 39 (revised 2007): guidance for temperature-controlled medicinal products: maintaining the quality of temperature-sensitive medicinal products through the transportation environment. Bethesda (MD): Parenteral Drug Association; 2007 (https://store.pda.org/ProductCatalog/Product.aspx?ID=1270, accessed 25 March 2015).

World Health Organization. Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical pharmaceuticals. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 9 (WHO Technical Report Series, No. 961; https://www.who.int/medicines/areas/quality_safety/quality_assurance/ModelGuidanceForStorageTransportTRS961Annex9.pdf?ua=1, accessed 10 February 2015).

REVISION HISTORY

Date	Change summary	Reason for change	Approved

ANNEX 3.

SHIPMENT INFORMATION CARD

Notes:

1. Card colour is to match the colours shown here: Pantone 279 ‘UN blue’ for type A/B, and Pantone 100 ‘light yellow’ for Type C.
2. With the exception of text in <arrow brackets>, manufacturers must use the exact wording shown in this annex.
3. The text enclosed in <arrow brackets> must be replaced with the appropriate product-specific name or description. Manufacturers are responsible for the correct translation of these passages.

CONTENTS

TYPE A/B (ENGLISH)

Mount device here
and this way up

Use only for OPV, BCG, Hib lyophilized, influenza seasonal (lyophilized), JE lyophilized, measles, MR, MMR, meningococcal A, meningococcal ACYW 135 (lyophilized), rabies (lyophilized), rotavirus (Bharat liquid and lyophilized – other than RotaTeq), rubella, varicella, yellow fever

SENDER

1. Prepare the shipping container.
2. Break off the twin label with bar code and stick it onto the shipping documents.
3. Activate <DEVICE NAME> by <describe activation procedure for device> with a start delay of 1 hour.
4. Complete the card below in ball point pen.
5. Insert this card, with the activated device attached, into the shipping container.
6. Seal the shipping container.

Supplier name: _____

Date: _____ Time: _____
dd.mm.yyyy hh:mm

Vaccine PO number: _____

Vaccine: _____

RECEIVER: Please return the card!

Front face

RECEIVER

1. On arrival, remove <DEVICE NAME> from the shipping container immediately.
2. <Describe stop procedure the device>.
3. Read the LCD display and follow the instructions as described below.

OK DISPLAY

<clearly illustrate OK screen display>

If OK, use vaccines normally.

ALARM DISPLAY

<clearly illustrate alarm screen display>

If <DEVICE NAME> displays alarm, proceed according to the decision table below:

Alarm temperature	What to do with vaccines	
	OPV	Other vaccines
>=45ºC	Contact procurement agency	Contact procurement agency
>=30ºC	Contact procurement agency	Contact procurement agency
>=10ºC	Contact procurement agency	Accept

Assembled and distributed by <company name and web address>

Back face

TYPE C (ENGLISH)

Mount device here
and this way up

Use only for DTP, DT, DTP-HepB-Hib, Hib (liquid), HepA, HepB, HPV, Influenza seasonal (liquid), IPV, JE (liquid), Meningococcal ACYW-135 (liquid), PCV, Rabies, TT, Td, OCV, PCV (other than Prevnar), RV (liquid and other than Bharat liquid)

SENDER

1. Prepare the shipping container.
2. Break off the twin label with bar code and stick it onto the shipping documents.
3. Activate <DEVICE NAME> by <describe activation procedure for device> with a start delay of 1 hour.
4. Complete the card below in ball point pen.
5. Insert this card, with the activated device attached, into the shipping container.
6. Seal the shipping container.

Supplier name: _____

Date: _____ Time: _____
dd.mm.yyyy hh:mm

Vaccine PO number: _____

Vaccine: _____

RECEIVER: Please return the card!

Front face

RECEIVER

1. On arrival, remove <DEVICE NAME> from the shipping container immediately.
2. <Describe stop procedure the device>.
3. Read the LCD display and follow the instructions as described below.

OK DISPLAY

<clearly illustrate OK screen display>

If OK, use vaccines normally.

ALARM DISPLAY

<clearly illustrate alarm screen display>

If <DEVICE NAME> displays alarm, proceed according to the decision table below:

Alarm temperature	What to do with vaccines
>=45ºC	Contact procurement agency
>=30ºC	Contact procurement agency
>=-0.5ºC	Conduct shake test. Use vaccines if passes. Inform procurement agency of test results

Assembled and distributed by <company name and web address>

Back face

TYPE RotaTeq® (ENGLISH)

Mount device here
and this way up

Use only for RotaTeq®

SENDER

1. Prepare the shipping container.
2. Break off the twin label with bar code and stick it onto the shipping documents.
3. Activate <DEVICE NAME> by <describe activation procedure for device> with a start delay of 1 hour.
4. Complete the card below in ball point pen.
5. Insert this card, with the activated device attached, into the shipping container.
6. Seal the shipping container.

Supplier name: _____

Date: _____ Time: _____
dd.mm.yyyy hh:mm

Vaccine PO number: _____

Vaccine: _____

RECEIVER: Please return the card!

Front face

RECEIVER

1. On arrival, remove <DEVICE NAME> from the shipping container immediately.
2. <Describe stop procedure the device>.
3. Read the LCD display and follow the instructions as described below.

OK DISPLAY

<clearly illustrate OK screen display>

If OK, use vaccines normally.

ALARM DISPLAY

<clearly illustrate alarm screen display>

If <DEVICE NAME> displays alarm, proceed according to the decision table below:

Alarm temperature	What to do with vaccines RotaTeq only
>=27ºC	Contact procurement agency
>=17ºC	Contact procurement agency
>=-25ºC	Contact procurement agency

Assembled and distributed by <company name and web address>

Back face

TYPE Prevnar® (ENGLISH)

Mount device here
and this way up

Use only for Prevnar®

SENDER

1. Prepare the shipping container.
2. Break off the twin label with bar code and stick it onto the shipping documents.
3. Activate <DEVICE NAME> by <describe activation procedure for device> with a start delay of 1 hour.
4. Complete the card below in ball point pen.
5. Insert this card, with the activated device attached, into the shipping container.
6. Seal the shipping container.

Supplier name: _____

Date: _____ Time: _____
dd.mm.yyyy hh:mm

Vaccine PO number: _____

Vaccine: _____

RECEIVER: Please return the card!

Front face

RECEIVER

1. On arrival, remove <DEVICE NAME> from the shipping container immediately.
2. <Describe stop procedure the device>.
3. Read the LCD display and follow the instructions as described below.

OK DISPLAY

<clearly illustrate OK screen display>

If OK, use vaccines normally.

ALARM DISPLAY

<clearly illustrate alarm screen display>

If <DEVICE NAME> displays alarm, proceed according to the decision table below:

Alarm temperature	What to do with vaccines Prevnar only
>=40°C	Contact procurement agency
>=30°C	Contact procurement agency
>=-0.5°C	Conduct shake test. Use vaccines if passes. Inform procurement agency of test results

Assembled and distributed by <company name and web address>

Back face

ANNEX 4.

SHAKE TEST PROTOCOL

CONTENTS

Purpose of the shake test

The shake test is designed to determine whether adsorbed vaccines with aluminum phosphate/hydroxide formulations have been affected by freezing.

How the shake test works

When a freeze-sensitive vaccine is solid frozen, hydrate water gets detached from the formulation and destructs the proton coat of adjuvant particles. This results in a decrease in the net positive electric charge as well as lowering of the Zeta potential value. Consequently, the destructed structure loses the ability to bind electric negative antigens and bovine serum albumin and, finally, the lattice structure between the adjuvant and the antigen becomes permanently broken.

Separated adsorbent tends to form granules that increase in particle size and weight and gradually settle to the bottom after the vial has been shaken. The size of the granules seems to increase after repeated freezing and thawing cycles. Sedimentation occurs faster in a like for like vaccine vial that has been frozen versus in a vaccine vial that has never been frozen.

Figure 1 Phase contrast microscopy findings in vaccines kept at optimum temperatures (left) and affected by freezing (right).

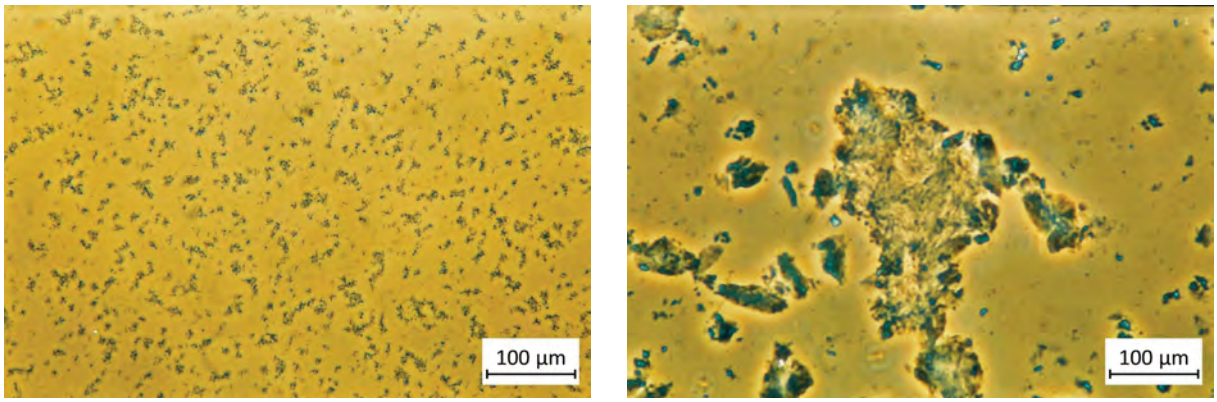
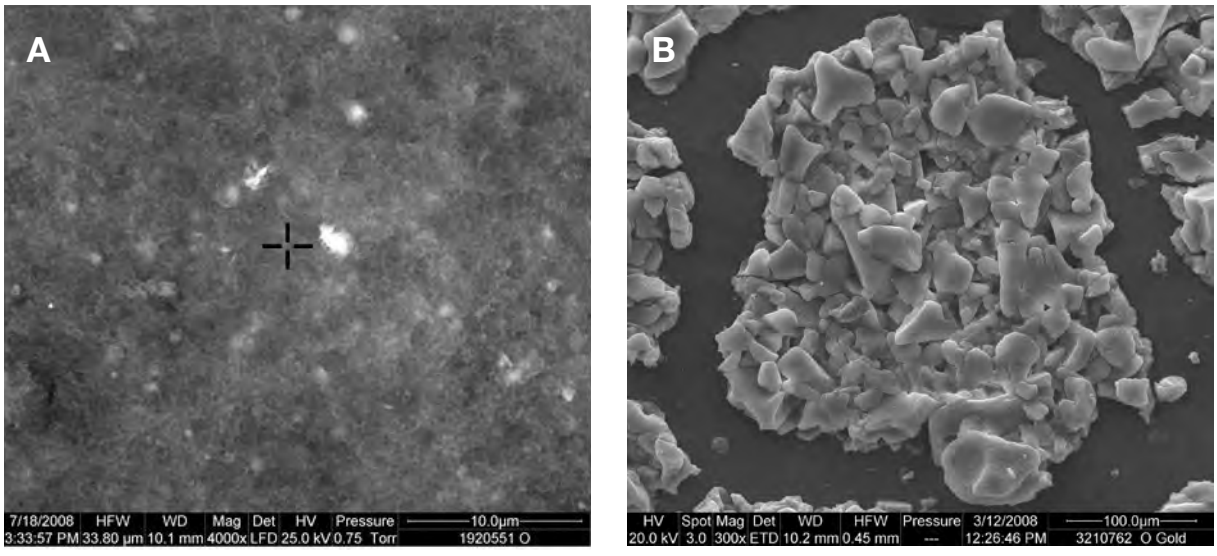


Figure 2 Scanning electron microscopy findings in vaccines kept at optimum temperatures (A) and affected by freezing (B).



At least one member of the duty personnel in every recipient country should know how to reliably and correctly perform and interpret the test for a vaccine shipment that has been exposed to freezing temperatures. A vaccine which fails the shake test should not be accepted. If exposure to freezing temperatures occurred in certain boxes of a multi-box shipment, the shake test should be conducted only for these boxes. In the case of a failed shake test, only these boxes should be rejected.

Application

The shake test has been validated by WHO through a double-blind cross-over study comparing the performance of the shake test conducted by trained health-care workers with that of phase contrast microscopy (PCM) as a “gold standard”. The shake test demonstrated 100% sensitivity (proportion of vials identified as freeze-damaged by the shake test among vials identified as freeze-damaged by PCM), 100% specificity (proportion of vials identified as non-frozen by the shake test among vials identified as non-frozen by PCM) and 100% positive predictive value (the probability that a vial is identified as freeze-damaged by the shake test is truly freeze-damaged) in this validation study. This confirms its validity for detecting freeze damage to aluminium-based freeze-sensitive vaccines.

The most recent studies with prequalified combination vaccines revealed that despite clear indication of freeze-damaged under PCM, it was not possible to differentiate freeze-damaged vaccines by the shake test for the Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenza type b vaccine (also marketed with labelled commercial name ComBE Five) by Biologicals E. Detailed analysis indicated that the conglomerates in frozen samples, although bigger than non-frozen particle size, was still much smaller compared to any other freeze-sensitive vaccines. This resulted in a sedimentation rate that is almost the same as the non-frozen samples. Since it was not certain for each and every vial to confirm whether it was affected by freezing, WHO has decided to highlight that the shake test is not applicable to this particular vaccine. This exception to the shake test covers all presentations of Biologicals E Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenza type b vaccine (1, 2, 5 and 10 doses) both liquid and two-vial set.

WHO recommends that in the case of any indication of freezing temperature exposure of Biologicals E Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenza type b vaccine, the vaccine must be rejected without any shake test.

When and how to do a shake test

If a temperature monitoring device in the shipping box shows a freeze alarm, then the shake test must be done to confirm the status of the vaccine. The Shake Test Protocol must be followed exactly as described below.

Individual batches of vaccine may behave differently from one another. Therefore, the procedure should be repeated with *all* suspect batches. Appropriate sampling methodology as set out in *Annex 5* should be followed to ensure that all of the damaged vaccine is identified and that none of this damaged vaccine is distributed or used.

The Shake Test need NOT be conducted under the following circumstances and shipment must be rejected:

- When solid frozen vaccine vial(s) have been found.
- With DTP and DTP containing vial(s) when a homogeneous solution CANNOT be obtained after vigorous shaking. In such cases, the white lumps or sediment cannot be separated from the walls of the glass vial. This happens only with DTP vials that have been exposed to sub- zero temperatures, but without freezing occurring.

Sampling incoming shipments for shake test

When vaccine arrives from the vaccine supplier it must be inspected and approved before it can be accepted into the country supply chain. International shipments arranged by UN procurement agencies will always have an electronic shipping indicator in each and every shipping container. Shipments ordered directly from an international or in-country manufacturer or supplier may not contain electronic or other freeze indicators.

CASE 1: When there is a shipping indicator in every container

a Mark and isolate any shipping container(s) where the electronic shipping indicator shows a freeze alarm. Keep the shipping containers in the cold chain.

b Inspect each suspect container individually following the sampling procedure described in *Annex* 5. Draw the correct number of sample vials from locations throughout the suspect container(s), including the middle of the container(s). Remember to prepare a frozen control sample for each individual vaccine batch.

c Send the shake test results to the vaccine supplier. In the case of UN-procured or donated vaccine, supply the shake test results to the relevant UN agency or to the donor for a final decision on what to do with the consignment.

d If the decision is taken to dispose of the vaccine, discard all vaccine in the affected container(s).

CASE 2: When there are no shipping indicators in the shipment, or if shipping indicators are not supplied in every container

a Mark and isolate the entire shipment but keep it in the cold chain.

b Follow the sampling procedure described in *Annex 5* for all vaccine in the shipment. Draw the correct number of sample vials from locations throughout the suspect shipment, including the middle of the container(s). Remember to prepare a frozen control sample for each individual vaccine batch.

c Send the shake test results to the vaccine supplier.

d If the decision is taken to dispose of the vaccine, discard all vaccine in the shipment.

Shake test protocol

Notes:
a This protocol must not be altered. There is only one correct way to conduct a Shake Test.
b The test procedure described below should be repeated with all suspect batches. In the case of international arrivals, the shake test should be conducted on a random sample of vaccine. However, if there is more than one lot in the shipment, the random sample must include a vial taken from each and every lot.

1. Take a vial of vaccine of the same type, manufacturer and batch number as the vaccine you want to test.

2. Clearly mark the vial as "FROZEN."

3. Freeze the vial in a freezer or the freezing compartment of a refrigerator until the contents are completely solid.

4. Let it thaw. Do NOT heat it!

5. Take your "TEST" vial from the batch that you suspect has been frozen.

6. Hold the "FROZEN" vial and the "TEST" vial together in one hand.

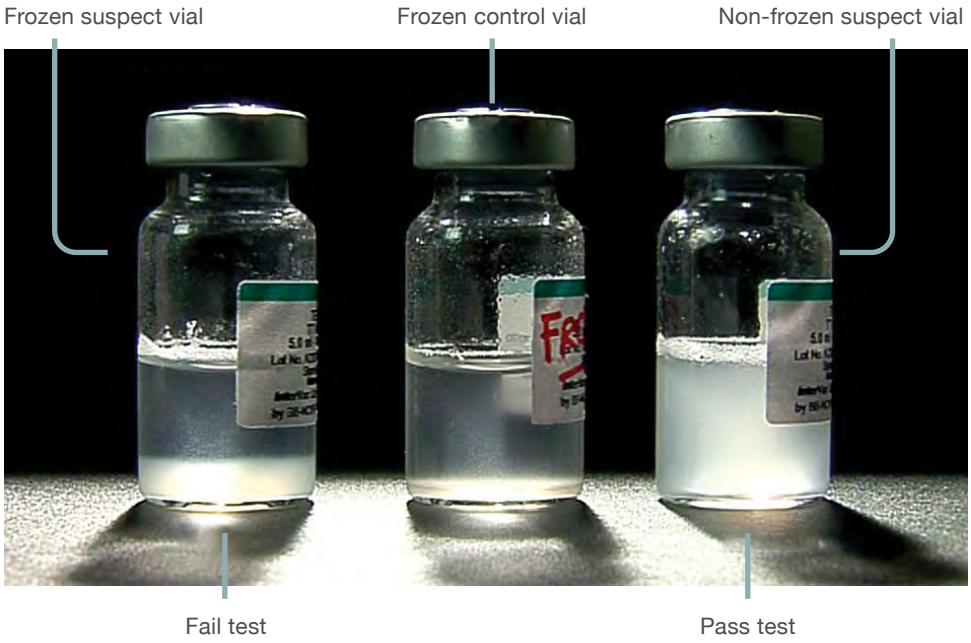
7. Shake both vials vigorously for 10-15 seconds.

8. Place both vials on a flat surface side-by-side and start continuous observation of the vials until the test is finished. (NOTE: If the vials have large labels which conceal the vial contents, turn both vials upside down and observe sedimentation in the neck of the vial.)

Use an adequate source of light to compare the sedimentation rates between vials.
if

9. The TEST vial sediments slower than the FROZEN vial, this is a PASS test. *then*	10. Sedimentation is similar in both vials *or* The TEST vial sediments faster than the FROZEN vial. This is a FAIL test. *then*
11. Use the vaccine batch.	11. Vaccine damaged: Notify your supervisor. Set aside all affected vaccine in a container marked "DAMAGED VACCINE FOR DISPOSAL– DO NOT USE"
	12. Discard all affected vaccine once you have received permission to do so
	13. Fill in the Loss/Adjustment Form.

Figure 3 Shake test with a fail and pass test results



ANNEX 5.

SAMPLING METHOD FOR SHAKE TEST

Every pharmaceutical system should have a quality control plan in place which describes the sampling procedure to be used in cases such as the one given in the example below.

This annex demonstrates how to use a quality control sampling system such as MIL-STD-1916. This USA military-standard has been used for many years as a sampling procedure. Other similar systems are also described by ANSI and ISO.

CONTENTS

Example of the sampling method

100 cartons of 10-dose HepB vaccine has been received, each carton containing 1,000 vials. In boxes #4, 7 and 27, the electronic shipping device indicated a freezing alarm.

Although the entire shipment consists of 100,000 vials, the shake test will be conducted only in boxes with a freezing alarm. In this case, we will conduct the shake test in three boxes (#4, 7 and 27) each containing 1,000 vials. It is not possible to do the shake test on all the vials and a representative sample must therefore be tested.

Assuming that all these boxes are from the same batch the following method can be used to calculate how many vials should be tested in order to indicate the status of the batch in these three boxes.

Notes on sampling

1. It is assumed that a 'normal' inspection level will be adequate (corresponding to verification level II).
2. For freeze sensitive vaccines, freezing is a *critical defect* and therefore the acceptance/rejection criteria will always be 0 and 1. This means that you can accept the shipment if zero vials in the sample fail the test, but you must reject the shipment if one or more vials in the sample fails.

Since all three boxes have 1,000 vials each, we will calculate the sampling size needed for one box and apply this to all three boxes.

Step 1: Refer to Table 1 of the Standard. Find the appropriate size range for the shipment in the *lot or batch size* column as shown in the example below.

Step 2: Find the matching sample size code in the *General Inspection Levels* column II as shown in the example.

Table 1 Code letters for entry into sampling tables, MIL-STD-1916.

Lot or production interval size	Verification levels						
	VII	VI	V	IV	III	II	I
2-170	A	A	A	A	A	A	A
171-288	A	A	A	A	A	A	B
289-544	A	A	A	A	A	B	C
545-960	A	A	A	A	B	C	D
961-1632	A	A	A	B	C	D	E
1633-3072	A	A	B	C	D	E	E
3073-5440	A	B	C	D	E	E	E
5441-9216	B	C	D	E	E	E	E
9217-17408	C	D	E	E	E	E	E
17409-30720	D	E	E	E	E	E	E
30721 and larger	E	E	E	E	E	E	E

As highlighted in the above table, the box size of 1000 vials corresponds to code letter D under normal inspection (verification level II).

Step 3: Use the below Table of the attributes sampling plans to determine sample size.

Table 2 Attributes sampling plans, MIL-STD-1916.

Code letter	Verification levels								
	T	VII	VI	V	IV	III	II	I	R
	Sample size (n_a)								
A	3072	1280	512	192	80	21	12	5	3
B	4096	1536	640	256	96	40	16	6	3
C	5120	2048	768	320	128	48	20	8	3
D	6144	2560	1024	384	160	64	24	10	4
E	8192	3072	1280	512	192	80	32	12	5

Notes:
When the lot size is less than or equal to the sample size, 100 percent attributes inspection of required.
One verification level (VL) to the left/right of the specified normal VL is the respective tightened/reduced plan.
Tightened inspection of VL-VII is T, reduced inspection of VL-I is R.

As highlighted in the above table, for a box of 1000 vials (code letter D), under normal verification levels (II), a randomly selection of 24 samples must be tested.

In all cases, non-conformity (failing shake test) should be zero for acceptance. If one vial out of 24 fails the shake test, that box (1000 vials) should be rejected. During a shake test, if a vial fails the shake test, all 24 samples do not need to be tested since the rejection criteria has already been obtained.

For further details on the sampling procedures, refer to http://bit.ly/2rFKOj4.

ANNEX 6.

DETAILED TEMPERATURE RECORDING DATA FOR SCENARIOS

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
1	4.5	4.5	-15.7
2	4.8	4.4	-15.4
3	5.0	4.5	-15.4
4	4.1	4.7	-15.2
5	4.2	5.0	-15.0
6	4.6	5.1	-15.1
7	4.9	4.8	-15.0
8	4.1	4.3	-15.0
9	4.1	4.5	-14.7
10	4.5	4.7	-14.6
11	4.8	4.9	-14.6
12	4.2	5.1	-14.5
13	4.0	5.2	-14.5
14	4.4	4.3	-14.4
15	4.7	4.4	-14.5
16	5.0	4.6	-14.4
17	4.2	4.8	-14.2
18	4.1	5.0	-14.0
19	4.4	5.2	-14.1
20	4.6	4.4	-14.0
21	4.8	4.4	-14.0
22	5.0	4.5	-13.6
23	4.7	4.7	-13.5
24	4.2	5.0	-13.4
25	4.4	5.1	-13.0
26	4.6	4.7	-12.8
27	4.8	4.3	-12.8
28	5.0	4.5	-12.0
29	5.1	4.7	-12.1
30	4.2	4.9	-11.8
31	4.3	5.1	-11.7
32	4.5	5.2	-11.8
33	4.7	4.4	-11.2
34	4.9	4.4	-10.9
35	5.1	4.6	-10.6
36	4.5	4.8	-10.5
37	4.2	5.0	-10.4
38	4.5	5.2	-10.0
39	4.7	4.6	-10.0
40	4.9	4.3	-9.3
41	5.1	4.5	-9.0
42	4.5	4.8	-8.4

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
43	4.2	5.1	-8.2
44	4.4	4.3	-7.9
45	4.7	4.3	-7.4
46	4.8	4.5	-7.5
47	5.1	4.7	-7.3
48	5.0	5.0	-7.0
49	4.2	4.5	-6.8
50	4.4	4.3	-6.7
51	4.6	4.6	-6.7
52	4.8	4.8	-6.3
53	5.0	5.1	-6.4
54	5.2	4.4	-6.1
55	4.3	4.4	-5.6
56	4.3	4.7	-5.3
57	4.5	5.0	-5.1
58	4.7	4.5	-4.6
59	4.9	4.4	-4.3
60	5.1	4.6	-4.4
61	4.6	4.9	-4.1
62	4.2	5.1	-3.8
63	4.4	4.2	-3.6
64	4.7	4.5	-3.3
65	4.8	4.8	-3.3
66	5.0	5.0	-3.0
67	5.1	4.5	-2.6
68	4.2	4.5	-2.7
69	4.4	4.8	-2.4
70	4.6	5.0	-2.3
71	4.8	4.3	-2.1
72	5.0	4.4	-2.0
73	5.2	4.7	-1.8
74	4.3	5.0	-1.7
75	4.3	4.4	-1.4
76	4.5	4.2	-1.3
77	4.7	8.1	-1.0
78	4.9	8.7	-0.8
79	5.1	8.7	-0.7
80	4.7	8.9	-0.5
81	4.2	8.7	-0.4
82	4.4	8.8	-0.2
83	4.7	8.9	-0.1
84	4.8	9.1	0.0

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
85	5.1	9.1	0.0
86	5.1	9.0	0.0
87	4.2	9.0	0.0
88	4.4	9.0	0.0
89	4.6	9.0	0.0
90	4.8	9.2	0.0
91	5.0	9.2	0.0
92	5.2	9.0	0.0
93	4.4	9.0	0.1
94	4.3	9.0	0.0
95	4.5	9.0	0.1
96	4.7	9.0	0.0
97	4.9	9.0	0.0
98	5.2	8.9	0.1
99	4.8	8.7	0.2
100	4.2	8.7	0.1
101	4.4	8.6	0.2
102	4.6	8.6	0.3
103	4.8	8.6	0.5
104	5.0	8.7	0.6
105	5.2	8.5	0.9
106	4.2	8.5	1.3
107	4.4	8.5	1.6
108	4.6	8.5	1.5
109	4.8	8.2	1.9
110	5.0	8.4	2.3
111	5.2	8.2	3.0
112	4.4	8.0	3.4
113	4.3	8.0	3.3
114	4.5	8.1	3.2
115	4.7	8.0	3.6
116	4.9	8.0	3.8
117	5.1	8.0	3.5
118	4.8	8.0	3.4
119	4.2	7.5	3.7
120	4.4	7.5	3.8
121	4.6	7.5	4.3
122	4.8	7.5	4.2
123	5.0	7.6	4.6
124	5.2	7.6	5.0
125	4.2	7.7	5.3
126	4.3	7.3	5.3

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
127	4.5	7.4	6.0
128	4.7	7.4	7.4
129	4.9	7.3	8.9
130	5.1	8.0	9.5
131	4.5	8.0	10.2
132	4.2	8.0	10.4
133	4.5	8.2	10.4
134	4.7	8.3	10.7
135	4.9	8.4	10.6
136	5.1	8.4	10.9
137	5.0	8.3	10.5
138	4.2	8.3	10.4
139	4.4	8.5	10.6
140	4.6	8.5	10.5
141	4.8	8.2	10.3
142	5.0	8.3	11.0
143	5.2	8.6	11.2
144	4.3	8.6	11.3
145	4.3	8.6	11.2
146	4.5	8.6	11.7
147	4.8	8.9	11.5
148	5.0	8.9	12.0
149	5.2	9.1	12.0
150	4.6	8.9	12.4
151	4.3	9.0	12.3
152	4.5	9.0	12.3
153	4.7	9.0	12.5
154	4.9	9.0	12.3
155	5.1	9.0	12.4
156	5.0	9.5	12.6
157	4.2	9.5	12.5
158	4.4	9.7	12.8
159	4.6	9.7	12.6
160	4.8	9.8	12.7
161	5.0	10.0	12.8
162	5.2	10.0	12.9
163	4.3	10.0	12.8
164	4.3	10.0	13.0
165	4.5	10.4	12.9
166	4.7	10.3	12.8
167	4.9	10.4	13.0
168	5.1	10.3	13.4

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
169	5.1	10.3	13.4
170	4.3	10.2	13.3
171	4.4	10.4	13.6
172	4.6	10.5	13.7
173	4.8	10.5	13.9
174	5.0	10.6	14.0
175	5.2	10.6	13.8
176	4.4	10.8	13.9
177	4.4	10.8	14.0
178	4.6	10.9	14.0
179	4.8	11.0	13.9
180	5.0	11.0	14.3
181	5.2	11.3	14.2
182	4.4	11.4	14.2
183	4.3	11.3	13.8
184	4.5	12.0	13.5
185	4.7	12.1	13.5
186	4.9	12.5	13.2
187	5.1	13.8	12.6
188	4.8	13.7	12.3
189	4.2	13.6	11.9
190	4.4	13.5	10.6
191	4.6	13.5	10.5
192	4.8	13.4	10.3
193	5.0	13.4	9.0
194	5.2	13.3	8.8
195	4.4	13.2	8.9
196	4.4	13.0	9.0
197	4.6	12.9	10.2
198	4.8	12.8	10.4
199	5.0	12.7	10.3
200	5.2	12.7	11.0
201	4.4	12.6	11.3
202	4.2	12.5	11.4
203	4.5	12.5	11.2
204	4.7	12.4	11.6
205	4.8	12.4	12.0
206	5.1	12.0	11.8
207	5.2	12.0	11.7
208	4.2	11.9	11.8
209	4.4	12.0	12.2
210	4.6	11.8	12.8

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
211	4.8	11.9	12.9
212	5.0	12.0	13.3
213	5.2	11.6	13.6
214	4.5	11.8	13.7
215	4.3	11.4	13.9
216	4.5	11.0	14.0
217	4.7	11.0	13.8
218	4.9	11.2	13.9
219	5.1	11.1	14.0
220	4.9	11.3	14.0
221	4.2	11.2	13.9
222	4.4	11.3	14.3
223	4.6	11.0	14.2
224	4.8	10.9	14.2
225	5.0	10.9	13.8
226	5.2	11.2	13.5
227	4.5	11.0	12.8
228	4.3	11.2	12.6
229	4.5	11.1	12.6
230	4.7	11.3	12.4
231	4.9	11.2	11.6
232	5.1	11.3	11.8
233	4.9	11.0	11.3
234	4.3	10.9	11.5
235	4.5	10.9	11.3
236	4.7	11.2	11.0
237	4.9	11.5	10.9
238	5.1	11.4	11.0
239	4.9	11.7	11.4
240	4.2	12.0	11.3
241	4.4	12.4	11.2
242	4.6	12.4	11.0
243	4.8	12.6	10.6
244	5.0	12.2	10.9
245	5.2	12.3	10.8
246	4.3	12.0	11.0
247	4.4	12.0	12.1
248	4.6	12.1	12.3
249	4.8	11.9	12.2
250	5.0	11.8	11.9
251	5.2	11.9	11.8
252	4.5	11.0	11.9

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
253	4.3	11.3	10.0
254	4.5	11.4	10.0
255	4.7	11.3	10.2
256	4.9	12.0	10.2
257	5.1	12.1	
258	4.9	12.5	
259	4.2	13.8	
260	4.4	13.7	
261	4.6	13.6	
262	4.8	13.5	
263	5.0	13.5	
264	5.2	13.4	
265	4.3	13.4	
266	4.4	13.3	
267	4.6	13.2	
268	4.8	13.0	
269	5.0	12.9	
270	5.2	12.8	
271	4.5	12.7	
272	4.2	12.7	
273	4.5	12.6	
274	4.7	12.5	
275	4.8	12.5	
276	5.1	12.4	
277	5.2	12.4	
278	4.3	14.0	
279	4.4	15.8	
280	4.5	15.9	
281	4.8	16.0	
282	4.9	16.0	
283	5.1	15.8	
284	5.0	15.8	
285	4.3	15.4	
286	4.5	15.6	
287	4.7	15.6	
288	4.8	15.8	
289	5.1	15.5	
290	5.2	15.5	
291	4.3	15.6	
292	4.4		
293	4.6		
294	4.8		

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
295	5.0		
296	5.2		
297	4.5		
298	4.3		
299	4.5		
300	4.7		
301	4.9		
302	5.1		
303	5.0		
304	4.2		
305	4.4		
306	4.6		
307	4.8		
308	5.0		
309	5.2		
310	4.5		
311	4.2		
312	4.5		
313	4.7		
314	4.8		
315	5.1		
316	5.0		
317	4.2		
318	4.4		
319	4.6		
320	4.8		
321	5.0		
322	5.2		
323	4.6		
324	4.3		
325	4.5		
326	4.7		
327	4.8		
328	5.1		
329	5.2		
330	4.3		
331	4.4		
332	4.6		
333	4.8		
334	5.0		
335	5.2		
336	4.5		

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
337	4.2		
338	4.4		
339	4.7		
340	4.8		
341	5.0		
342	5.2		
343	4.3		
344	4.3		
345	4.5		
346	4.7		
347	5.0		
348	5.1		
349	5.0		
350	4.2		
351	4.4		
352	4.6		
353	4.8		
354	5.0		
355	5.2		
356	4.5		
357	4.4		
358	4.5		
359	4.7		
360	5.0		
361	5.1		
362	4.8		
363	4.3		
364	4.5		
365	4.7		
366	4.9		
367	5.1		
368	5.2		
369	4.3		
370	4.4		
371	4.6		
372	4.8		
373	5.0		
374	5.2		
375	4.4		
376	4.4		
377	4.5		
378	4.7		

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
379	5.0		
380	5.1		
381	4.7		
382	4.3		
383	4.5		
384	4.7		
385	4.9		
386	5.1		
387	5.2		
388	4.4		
389	4.4		
390	4.6		
391	4.8		
392	5.0		
393	5.2		
394	4.6		
395	4.3		
396	4.5		
397	4.8		
398	5.1		
399	4.3		
400	4.3		
401	4.5		
402	4.7		
403	5.0		
404	4.5		
405	4.3		
406	4.6		
407	4.8		
408	5.1		
409	4.4		
410	4.4		
411	4.7		
412	5.0		
413	4.5		
414	4.4		
415	4.6		
416	4.9		
417	5.1		
418	4.2		
419	4.5		
420	4.8		

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
421	5.0		
422	4.5		
423	4.5		
424	4.8		
425	5.0		
426	4.3		
427	4.4		
428	4.7		
429	5.0		
430	4.4		
431	4.2		
432	8.1		
433	8.7		
434	8.7		
435	8.9		
436	8.7		
437	8.8		
438	8.9		
439	9.1		
440	9.1		
441	9.0		
442	9.0		
443	9.0		
444	9.0		
445	9.2		
446	9.2		
447	9.0		
448	9.0		
449	9.0		
450	9.0		
451	9.0		
452	9.0		
453	8.9		
454	8.7		
455	8.7		
456	8.6		
457	8.6		
458	8.6		
459	8.7		
460	8.5		
461	8.5		
462	8.5		

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
463	8.5		
464	8.2		
465	8.4		
466	8.2		
467	8.0		
468	8.0		
469	8.1		
470	8.0		
471	8.0		
472	8.0		
473	8.0		
474	7.5		
475	7.5		
476	7.5		
477	7.5		
478	7.6		
479	7.6		
480	7.7		
481	7.3		
482	7.4		
483	7.4		
484	7.3		
485	8.0		
486	8.0		
487	8.0		
488	8.2		
489	8.3		
490	8.4		
491	8.4		
492	8.3		
493	8.3		
494	8.5		
495	8.5		
496	8.2		
497	8.3		
498	8.6		
499	8.6		
500	8.6		
501	8.6		
502	8.9		
503	8.9		
504	9.1		

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
505	8.9		
506	9.0		
507	9.0		
508	9.0		
509	9.0		
510	9.0		
511	9.5		
512	9.5		
513	9.7		
514	9.7		
515	9.8		
516	10.0		
517	10.0		
518	10.0		
519	10.0		
520	10.4		
521	10.3		
522	10.4		
523	10.3		
524	10.3		
525	10.2		
526	10.4		
527	10.5		
528	10.5		
529	10.6		
530	10.6		
531	10.8		
532	10.8		
533	10.9		
534	11.0		
535	11.0		
536	11.3		
537	11.4		
538	11.3		
539	12.0		
540	12.1		
541	12.5		
542	13.8		
543	13.7		
544	13.6		
545	13.5		
546	13.5		

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
547	13.4		
548	13.4		
549	13.3		
550	13.2		
551	13.0		
552	12.9		
553	12.8		
554	12.7		
555	12.7		
556	12.6		
557	12.5		
558	12.5		
559	12.4		
560	12.4		
561	14.0		
562	15.8		
563	18.2		
564	19.6		
565	20.3		
566	20.5		
567	20.5		
568	20.3		
569	20.2		
570	21.0		
571	21.0		
572	22.0		
573	22.0		
574	23.0		
575	23.0		
576	23.0		
577	23.6		
578	23.7		
579	24.2		
580	24.3		
581	26.0		
582	26.7		
583	26.8		
584	26.6		
585	27.0		
586	27.3		
587	27.5		
588	27.5		

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
589	28.3		
590	28.4		
591	28.8		
592	30.0		
593	30.6		
594	30.7		
595	30.5		
596	31.0		
597	31.0		
598	31.4		
599	31.3		
600	31.2		
601	31.4		
602	31.4		
603	31.3		
604	31.2		
605	31.7		
606	31.4		
607	31.3		
608	31.2		
609	31.4		
610	31.2		
611	31.6		
612	31.7		
613	31.4		
614	31.7		
615	31.8		
616	31.6		
617	31.9		
618	31.9		
619	31.9		
620	32.0		
621	32.0		
622	32.0		
623	31.8		
624	31.9		
625	31.7		
626	31.7		
627	31.4		
628	31.7		
629	31.8		
630	31.6		

Measurement no	SCENARIO 1	SCENARIO 2	SCENARIO 3
631	31.9		
632	31.9		
633	31.5		
634	31.6		
365	31.5		
636	31.2		
637	31.0		
638	31.0		
639	31.0		
640	30.8		
641	30.9		
642	31.0		
643	31.0		
644	31.5		
645	31.0		
646	31.0		
647	31.4		
648	31.4		
649	31.6		
650	31.6		
651	31.4		
652	31.3		
653	31.3		
654	31.5		
655	31.0		
656	31.0		
657	30.8		
658	30.9		
659	30.7		
660	31.0		
661	31.0		
662	31.0		

ANNEX 7.

VACCINE ARRIVAL REPORT (VAR)

CONTENTS

Vaccine Arrival Report (VAR)

This report is to be filled in by authorized staff, ratified by the Store Manager or the EPI Manager, and forwarded to UNICEF within three working days of vaccine arrival. Use one report for each vaccine in the shipment.

COUNTRY	
REPORT No.	

Date of report	

Place, date and time of inspection	Name of cold store, date and time vaccines entered into cold store

PART I — ADVANCE NOTICE

MAIN DOCUMENTS	Date received by consignee	Copy airway bill (AWB)	Copy of packing list	Copy of invoice	Copy of release certificate
Pre-advice shipment notification		Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

List other documents (if requested)	

PART II — FLIGHT ARRIVAL DETAILS

AWB Number	Airport of destination	Flight No	ETA as per notification		Actual time of arrival	
			Date	Time	Date	Time

NAME OF CLEARING AGENT: _____ ON BEHALF OF: _____

PART III — DETAILS OF VACCINE SHIPMENT

Purchase Order No.	Consignee	Vaccine description (Type and doses/vial)	Manufacturer	Country

Vaccine				Diluent/droppers			
Lot Number	Number of boxes	Number of vials	Expiry date	Lot Number	Number of boxes	Number of units	Expiry date

(Continue on separate sheet if necessary)

	Yes	No	Comments
Was quantity received as per shipping notification?	☐	☐	
If not, were details of short-shipment provided prior to vaccine arrival?	☐	☐	

No. = Number
WHO recommends all UN agencies, countries and non-governmental organizations procuring vaccines adopt this report.

Report No.	

PART IV — DOCUMENTS ACCOMPANYING THE SHIPMENT

Invoice	Packing list	Release certificate	Vaccine Arrival Report	Other
Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	
Comments				

PART V — STATUS OF TEMPERATURE MONITORING DEVICES and COOLANTS

Total number of boxes inspected:	
Coolant type:	Dry ice ☐ Icepacks ☐ No coolant ☐
Temperature monitors present:	VVM ☐ Cold-chain monitor card ☐ Electronic device ☐ Type: _____

PROVIDE BELOW DETAILS OF STATUS ONLY WHEN PROBLEMS ARE OBSERVED
(in addition fill in ALARM REPORTING FORM if there are any ALARMS in electronic devices):

Box Number	LOT NO	Alarm in electronic device				Cold-chain monitor				Date/time of inspection
		>=45^{0}C	>=30^{0}C	>=10^{0}C	<=-0.5^{0}C	A	B	C	D	

(Continue on separate sheet if necessary)

Note: For shipments of certain types of PCV and Rotavirus, alarm settings on the temperature monitor device may be different than those listed above. If different alarms are recorded, please provide comments in General Conditions of Shipment section.

PART VI — GENERAL CONDITIONS OF SHIPMENT

What was the condition of boxes on arrival?	
Were necessary labels attached to shipping boxes?	
Other comments including description of alarms in electronic devices: (continue on separate sheet if necessary)	

PART VII — NAME AND SIGNATURE

Authorized Inspection Supervisor _____ DATE _____ Central store or EPI Manager _____ DATE _____

For UNICEF Country Office use only

Date received by Country Office: _____ **Contact Person**:_____

Guidelines for completing the Vaccine Arrival Report

The Vaccine Arrival Report (VAR) is a comprehensive record of cold-chain conditions during transport and of required compliance with shipping instructions. Recipient governments and procurement agencies (UNICEF country offices, UNICEF Supply Division, PAHO Revolving Fund), are responsible for the report, and for taking appropriate action if problems are reported (e.g. follow-up with the manufacturer, forwarding agent, WHO, etc.).

Use one report form for each shipment and for each vaccine in the shipment. In the case of short-shipments (where parts of the original quantities are not delivered), complete a separate report for each part delivered.

Complete the form as described below. In the **header boxes** at the top of the form, enter the name of the recipient country, the report number, and details of place and date of inspection and storage. The **report number** is an internal number for organizing records; compile it as follows: country code; year; number for each report (e.g. BUR–2005–001 for one vaccine; BUR–2005–002 for a second vaccine, etc.). In the case of a short-shipment, the numbers for the separate deliveries would be, for example, BUR–2005–003.1, BUR-2005-003.2, etc.

Part I — Advance notice

I.1 Enter dates and details of documents received in advance of the vaccine shipment.

Part II — Flight arrival details

II.1 Fill in details of expected and actual arrival times for the shipment.

II.2 Fill in the name a) of the clearing agent and b) for whom the agent acts (e.g. the Ministry of Health, UNICEF or WHO).

Part III — Details of vaccine shipment

III.1 Fill in details of the order (purchase order number, consignee, vaccine description etc.).

III.2 For each batch of vaccine included in the shipment, record:
a) the number of shipping boxes;
b) the number of vials;
c) the expiry date.

The number of boxes you enter should always match the number of boxes shown in the packing list. If it does not, note under *Comments* if advance notice of a change in the quantity was provided. It is not necessary to count the number of individual vaccine packs in each shipping box for this report.

III.3 For the diluents and droppers (if included) in the shipment, record:
a) the number of shipping boxes;
b) the number of vials;
c) the expiry date.

The information for III.2 and III.3 is also in the packing list.

Note: Diluents for freeze-dried vaccine and droppers for oral polio vaccine (OPV) are integral parts of the vaccine, so always include them on the same form. If diluent/droppers are delivered separately, consider it a short-shipment.

Part IV — Documents accompanying shipment

The packing list should indicate which box contains the shipping documents (usually Box 1).

IV.1 If this information is not included in the packing list or in documents sent separately by courier, pouch or other means, note this under *Comments*.

IV.2 Verify that all necessary documents are present and complete the form accordingly.

Note: If the lot release certificate is missing, do not use the vaccines; keep them on hold in cold storage until the relevant document has been obtained from the vaccine manufacturer.

PART V – Status of temperature monitoring devices and coolants

Inspect the temperature monitors in all boxes before putting vaccines into cold storage. For very large shipments, or when immediate storage in the shipping boxes is required, check a representative number of boxes before placing the shipment in the cold store. Complete inspection of all boxes the next day, or as soon as possible thereafter; under *Comments*, note the date and time when the complete inspection took place.

Note: In this report, enter the information below (V.1) *only* for boxes in which the temperature monitor shows a change that indicates potential damage to vaccines (alarm indication in the electronic device, or cold-chain monitor card as per vaccine/threshold table in card). Electronic alarm report form should be filled in case of alarms.

V.1 Enter:
a) the number of boxes inspected (this should equal the total number in the shipment);
b) the type of coolant used;
c) details of any temperature exposure detected.

V.2 Photocopy or scan LCD screens in electronic devices that show alarm status and attach to the report.

V.3 Clearly identify vaccines in boxes in which the indicator shows exposure to temperatures that risk damage and keep them in the cold room for further assessment of their condition. **Do not discard vaccines until assessment is completed.**

PART VI — General conditions of shipment

VI.1 Indicate if the shipping boxes were received in good condition and if all necessary labels on the outside of the shipping boxes were present; add any comments.

PART VII — Name and signature

VII.1 The authorized person responsible for the inspection and the Central Store Manager or the EPI Manager should sign this report.

VII.2 Send the form, completed and signed, to the UNICEF within three working days of arrival of the vaccine.

Electronic Alarm Report Form

Reporting alarm details in UNICEF international vaccine shipments

A special form has been designed for the purpose of reporting alarm details displayed in electronic devices. This form should **ONLY** be filled in if any alarms have occurred, and should be attached to the Vaccine Arrival Report (VAR). A clear photocopy and/or printed copy of the scanned image of the electronic devices displaying alarm status should be attached to this form.

Country:		**Date of Report:**	
Vaccine:		**Compiled by:**	

Type of device Q-Tag2Plus ☐ Q-Tag Clm ☐ VaxAlert ☐
TIC20 ☐ Other ☐ If OTHER, specify: _____

Box No	Serial No	Time stopped	Elapsed transit time	>=45ºC 1 hour		>=30ºC 10 hrs		>=10ºC 20 hrs		<=-0.5ºC 1 hr		Other	
				Time	ºC	Time	ºC	Time	ºC	Time	ºC	Time	ºC

***Note**: For shipments of certain types of PCV and Rotavirus, alarm settings may be set at different thresholds than those listed on the VAR and alarm reporting form. In the case of these alarms, please comment in "Other" column. Use additional pages if necessary.*

Guidelines for completing the Electronic Device Alarm Report Form

Country	Enter name of the country
Date of report	Enter date of report
Type of device	Mark the type of device by ticking the appropriate box
Type of vaccine	Enter the type of vaccine, e.g. BCG, OPV, HepB, etc.
Box number	Write the number of the box (carton) that the electronic device was taken out of, e.g. 001, 002…099.
Serial number	Write down the serial number of the electronic device from the bar code/serial number, e.g. 10000001
Time stopped	Enter the local time you stopped this particular device in 00hrs:00min format
Elapsed transit time	Enter elapsed transit time
Time	Enter time displayed in HISTORY mode for each alarm.
ºC	Enter minimum or maximum temperatures displayed for each alarm, e.g. 34.7ºC, 13.5ºC, or -0.5ºC

If any of the alarms are repeated in the same electronic device, enter this information in a new row.

If the device has USB, data should be downloaded and included in the submission of electronic alarm report form.

ANNEX 8.

PAHO FORM 183 - CONFIRMATION OF ARRIVAL OF SHIPMENTS

CONTENTS

PAHO 183 (1-02) PAGE/PAGINA:

PAN AMERICAN HEALTH ORGANIZATION
Regional Office of the
World Health Organization
Procurement Services (PRO)
525 Twenty-third Street, N.W., Washington, D.C. 20037
Telephone (202) 974-3433
Fax: (202) 974-3615
E-Mail: PRO@paho.org

PURCHASE ORDER

No: APO
Date:

Confirmation of Arrival of Shipment
Confirmación de la Llegada del Embarque

Dear Sir/Madam,

We hereby confirm the arrival of the following shipment:

Estimados Señores,

Por la presente confirmamos la llegada del siguiente embarque:

Order Number *Orden Número*	AWB *Guía aérea*	Pieces *Bultos*	Weight *Peso*	Date of arrival *Fecha de llegada*	Complete shipment *Embarque completo*
					☐

The shipment was received at: / *El embarque fue recibido en*:

- ☐ Airport / *Aeropuerto*
- ☐ Port / *Puerto*
- ☐ Customs Warehouse / *Bodega de la aduana*
- ☐ Consignee's facility / *Bodega del consignatario*

Name/Signature/Title/Date

Nombre/Firma/titulo/Fecha

Please mark the last column if the shipment was received complete.

Sírvase marcar la última columna si el embarque llego completo.

Please send this confirmation to your counterpart at PAHO/WHO Representative Office.

Agradecemos enviar esta confirmación a su contraparte en la representación de la OPS/OMS.

Acknowledgement of Shipment Arrival. Within 24 hours of the shipment's arrival at the destination airport, the consignee must acknowledge via email the arrival of goods to PAHO's Country Office. Acknowledgement does not imply acceptance of the goods; it simply indicates arrival of the goods. Therefore, acknowledgement should not be delayed pending final determination of acceptance. If subsequently the goods are found to be damaged or incomplete, the prior acknowledgment of arrival will not interfere with the claim process, provided the claim is reported within 72 hours of the delivery of the shipment.

Confirmation of Arrival. The consignee will confirm arrival of shipment by filling electronically or by hand PAHO Form 183 (the last page of the purchase order) or a statement written on the consignee's letterhead. The consignee will email this form to the PAHO Country Office Procurement Focal Point. This acknowledgement will reference the purchase order (PO) number, AWB information, date of arrival and any remarks about the shipment conditions on the bottom of the form. The clearance and claim of vaccines from customs facilities must be immediate.

Delayed Arrival. Consignees shall acknowledge vaccines' arrival as described above. For shipments that have not arrived within 24 hours after the date indicated in the shipping details, the consignee will initiate tracing of shipments locally with the responsible airline or freight agent. The consignee immediately will notify the PAHO Country Office, via email.

Verification of Shipment. Complete verification of vaccines shipments will take place within 72 hours of delivery. Verification means the act of opening boxes and confirming that the contents are in good order. The consignee also will inform the PAHO Country Office of any alarm being displayed on temperature monitors or if monitors are not included in shipment as required.

Instructions for temperature excursion of biological products.

The consignee should take the following actions:

1. Ensure that the shipment is maintained at storage conditions recommended by the manufacturer.
2. Verify the condition of the shipment and stop the electronic temperature monitors.
3. Retain electronic temperature monitors.
4. If the electronic temperature monitors have set off an alarm, send to the PAHO Country Office procurement focal point the data to support the temperature excursion.
5. Segregate the insulate shipping units where temperature excursion occurred from others.
6. PAHO will advise the Member State of the recommendation of product use

ANNEX 9.

PAHO CLAIM REPORT

CONTENTS

Pan American Health Organization (PAHO/WHO)
Regional Office of the World Health Organization
Office of Procurement
525 23rd Street N.W.
Washington, DC
20037
Telephone: 202-974-3000

PURCHASE ORDER

NO:
Date:

CLAIM REPORT / *REPORTE DE RECLAMO*

PART I – DETAILS OF THE SHIPMENT / *DETALLES DEL EMBARQUE*

Country/ *País*	Click here to enter text.
Consignee / *Consignatario*	Click here to enter text.

Date of report *Fecha del evento*	Click here to enter a date.

Claim category / *Tipo de reclamo*

1.	**Temperature excursions / *Excursión de temperatura* ***	☐
2.	**External damage / *Daño externo*** Attach photo / *adjuntar fotos*	☐
3.	**Internal damage / *Daño interno*** Attach photo / *adjuntar fotos*	☐
4.	**Missing quantity / *Cantidad faltante***	☐
5.	**Wrong item or presentation / *Producto, o presentación equivocada***	☐
6.	**Quality Component / *Por componente de calidad***	☐

*For excursion of temperature, please proceed directly to Part II of this form and fill out all fields.
Si el reclamo es por excursión de temperatura, por favor seguir directamente para la Parte II de este formato de reclamos y llenar todos los campos.

Commercial name, dose, presentation (Tablets, Capsule, solution, Injectables) *Nombre comercial, dosis, presentación (ej.: tabletas, capsulas, solución inyectable)*	Click here to enter text.
Supplier / *Proveedor*	Click here to enter text.
Airway bill / *Guía aérea*	Click here to enter text.

Description of the event / *Descripción del evento*
Click here to enter text.

Pan American Health Organization (PAHO/WHO)
Regional Office of the World Health Organization
Office of Procurement

525 23rd Street N.W.
Washington, DC
20037
Telephone: 202-974-3000

PURCHASE ORDER

NO:
Date:

PART II – TEMPERATURE SENSITIVE PRODUCTS / *PRODUCTOS PERECEDEROS*

* Required fields for biologic products / *Campos obligatorios para productos biológicos*

Supplier *Proveedor* *	**Product name** *Nombre del producto* *	**Target Population (vaccines)** *Población (vacuna)**	**Product presentation** *Presentación del producto* *	**Type of Primary Container** *Tipo de envase primario* *	**Type of monitor** *Tipo de monitor* *
Click here to enter text.	Click here to enter text.	☐ Adult ☐ Pediatric ☐ Other	☐ Single / Unidosis ☐ Multi dosis ☐ Other	☐ Vial ☐ Prefilled syringe /Jeringas prellenas) ☐ Ampoule /*Ampolla* ☐Other / *Otro*	Click here to enter text.

Does the shipment have diluents? / *Hay diluyentes en el embarque?*	**Yes** / *Si* ☐ **No** ☐
Was the diluent included in same package with product? / *Fueron los diluyentes incluidos con el producto en el mismo empaque?*	**Yes** / *Si* ☐ **No** ☐
Record storage temperature recommended in the label of the diluents if they were transported in separate boxes / *Indique la temperatura de almacenamiento recomendada en el etiquetado de los diluyentes si fueron transportados en cajas separadas*	

QUANTITY / *CANTIDAD* *	**TOTALS** *
Number of doses or units received *Numero de dosis o unidades recibidas* *	Click here to enter text.
Number of Boxes in shipment *Numero de cajas en el embarque* *	Click here to enter text.
Number of boxes with alarmed monitors *Numero de cajas con alarma en los monitores* *	Click here to enter text.
Number of boxes without temperature monitors *Numero de cajas sin monitores de temperatura* *	Click here to enter text.

REPORTING CLAIMS OF TEMPERATURE EXCURSIONS, DAMAGED OR MISSING ITEMS AND QUALITY

Introduction

Claims can arise from quality inadequacy or as a result of damage, packing shortages or the loss of a good arriving at destination.

For procurement on behalf of a Member State, the final consignee has the responsibility of reporting a claim of any nature within three working days of the delivery.

The PAHO Country Office Procurement Focal Point will coordinate communication between PAHO Headquarters (HQ) and the Member State regarding the processing and resolution of a claim. PAHO (HQ) Procurement Office will support resolution of a claim with a vendor and technical counterparts.

Instructions for quality claims

Examples:

- Foreign particles inside the vials or change in physical appearance.
- Detaching labels from vials.

Information required:

1. Location where product is stored.
2. Storage conditions of the location where the product is stored.
3. Lot numbers and number of vials that present this problem.
4. Number of vials received/ number of vials inspected/ number of vials remain available.
5. Temperature records from arrival of shipment in the country to date.
6. Pictures that show that quality deviation reported.
7. Indicate if product has been distributed and quantity distributed per location.

REVISION HISTORY

2020 edition of the *Guidelines on the international packaging and shipping of the vaccines* comes with substantial revisions compared to 2005 edition. Some of these revisions are modifications while others are additions.

These changes are listed in the following table.

Page	Section	Change/addition	Reason
6	Abbreviations	New abbreviations are added	New abbreviations
8	Glossary	Illustrated glossary of key terminology used and/or referred in the guidelines	New section
14	Introduction	Recommendation of risk assessment to be conducted by all involved parties in international shipment of vaccines to assess potential risks to quality and integrity of vaccines during air freight and receipt operations.	New section
16	Insulated packaging standards	Table 1 is updated with new prequalified vaccines	Abandoning the stress test. New prequalified products
18	Use of coolants in international air shipments	Recommendations on type of coolants to be included in the international air shipments	New section
20	General packaging criteria	Design of shipping containers	New section
21	Insulated pallet shippers	Conditions on the use of pallet shippers	New section
22	Cargo covers	Cargo covers as additional risk mitigation approach	New section
23	Active vs. passive air shipment systems	Conditions on the use of active systems for air shipments	New section
24	Transport route profiling and qualification of shipping containers	Abandoning the stress testing at 43°C and at -5°C for 48 hours, vaccine manufacturers are now required to produce transport route profiling data and use degree-hour calculations to derive a test profile, and then apply this as a basis for conducting operational qualification (OQ) of packaging solutions under laboratory conditions in temperature-controlled test chamber (using the test profile derived from degree- hour calculations).	New section
29	Table 3. Specifications of the electronic shipping indicators	More details are added to the specifications of the electronic shipping indicators.	More detail added
30	Table 3. Specifications of the electronic shipping indicators	Recording period is revised as 40 days (previously 10 days or 20 days). Accordingly recording interval is doubled from 10 min to 20 min.	In order to cover all routes including problematic ones with one device.
30	Electronic data integrators for international shipments	Optional USB interface or equivalent interphase to download a time-temperature data and graph	Optional USB interface added

Page	Section	Change/addition	Reason
30	Electronic data integrators for international shipments	Type 1 and type 2 devices are now named as Type C and type A/B.	Matching the ABC classification of packaging
31	Table 4 through 7	List of vaccines for Type A/B and type C devices are updated	Updated with new prequalified vaccines
33	The impact of high temperatures on the stability time of vaccines, as indicated by high temperature alarms	The impact of temperature alarms on shelf life of vaccines are explained with the help of three scenarios.	New section
39	Temperature excursions with no alarm	Recommendations on how to handle temperature excursions with no alarm	New section
39	Interpreting VVM in international shipments	All possible readings from an electronic data integrator are explained from VVM perspective	New section
42	Volume per dose and bulking factors for calculating necessary storage	To keep the list updated, package dimensions for calculation of volume per dose and bulking factors, WHO now offers a spreadsheet via a download link. In order to reduce the volume per dose, VPAGG recommendations to vaccine manufacturers are included.	Current figures are now offered in spreadsheet through a download link. VPAGG recommendations on reducing the volume per dose and bulking factors are included.
44	Labelling for international shipments	More details are added. Expiry date on all labels should be written in MM.YYYY format	Harmonization with prequalification guidelines
45	Figure 6. IATA time and temperature sensitive label	New IATA time and temperature sensitive label	New section
46	Figure 7. Class 9 hazard label	Class 9 hazard label for dry ice shipments	New section
46	“Vaccine rush” label	Deleted	Deleted
47	Barcoding	New information since UNICEF tenders issued after 1 October 2019 and to be implemented as of 31 December 2021 at the latest, UNICEF is now requiring bar-codes.	New section
48	International shipping procedures	More details are added. PAHO related information is now included.	Expanded with more detailed information PAHO related information is added
54	References	Critical documents and links (where available) are added as resource materials	New section
56	Annex 1. Transport route profiling qualification	Full reproduction of the document	New section
86	Annex 2. Qualification of shipping containers	Full reproduction of the document	New section
112	Annex 3. Shipment information card	Revised shipment information cards based on new vaccines added to the list	New section
118	Annex 4. Shake test protocol	Expanded with more information and photographs. New information is added for the only Al adjuvanted vaccine that the shake test is not applicable.	Expanded with more information
126	Annex 5. Sampling method for shake test	Recommended sampling method and acceptance criteria for shake test	New section

Page	Section	Change/addition	Reason
130	Annex 6. Detailed temperature recording data for scenarios	Full data set of three scenarios for “the impact of triggered alarms on shelf life of vaccines” chapter	New section
148	Annex 7. Vaccine arrival report, PART V	PART V title change	Since VVM is not a shipping indicator, title of this section is now changed to “status of temperature monitoring devices and coolants”
154	Annex 8. PAHO form 183 – confirmation of arrival of shipments	In refer to “International shipping procedures” chapter	New form
158	Annex 9. PAHO claim report	In refer to “International shipping procedures” chapter	New form
2005 edition page 22	Annex 3: List of contact points for national regulatory authorities in countries producing vaccines prequalified for purchase by United Nations agencies	Deleted	Deleted (this information is for vaccine manufacturers and is already known)

PHOTOGRAPHY CREDITS

Mohannad Abdo – page 8 *(bar code).*

Daniel De Vincentis – page 8 *(Blow-fill-seal container).*

Umit Kartoglu – page 8 *(dunnage)*; page 12 *(vaccine vial monitor)*; page 18; and page 122.

PQS archives – page 8 *(electronic data integrator)*; page 9 *(electronic data logging monitor)*; page 12 *(tertiary pack or carton)*; page 21.

Andrea Crisante, Shutterstock – page 9 *(EURO pallet)* and page 10 *(pallet).*

nacykoa43, Shutterstock – page 10 *(pallet).*

Extensio et Progressio archives – page 10 *(pallet shipper)*; page 120.

PATH – page 10 *(primary container).*

Gencer Yurttas – page 12 *(shelf life).*

DuPont Protection Solutions – page 22.

Umit Kivanc – page 125.

World Health Organization

Department of Regulation and Prequalification (RPQ)

World Health Organization
CH-1211 Geneva 27
Switzerland
Email: vaccprequalification@who.int
or visit our website at: https://extranet.who.int/pqweb/vaccines

The Access to Medicines and Health Products (MHP) Division works with Member States and partners to improve the access to safe, quality assured, efficacious and affordable medicines and health products and to promote that these are used rationally. In line with the GPW 13 strategic priorities and to achieve greater country impact, the RPQ Department works with the Health Product Policy and Standards (HPS) Department in the MHP division in the wider framework of access to medicines and health products and Universal Health Coverage and cooperates with the

disease-oriented programmes (among others HIV/AIDS, TB, malaria, NCDs and mental health, reproductive health and maternal and child health, immunization) and health systems oriented programs such as Primary Health Care. The department works with a wide range of UN organizations, international partners, expert networks and WHO Collaborating Centres.

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