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

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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.

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

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.

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.

[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.

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.

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 sections 6.8.1, 6.8.3 and 6.8.4 of the WHO Technical Report Series No. 961, 2011, Annex 9: *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.[4] The document covers the qualification of all single-use and reusable active, passive, hybrid, and cryogenic dry/vapour shipping containers or systems used for the transport of a time- and temperature-sensitive pharmaceutical product (TTSPP) in external distribution.

The principal focus is on performance qualification (PQ). The document also includes a brief introduction to the requirements and technical resources needed for design qualification (DQ) and operational qualification (OQ) because these activities need to be understood by those responsible for assessing and procuring third-party container systems. The supplement should be read in conjunction with the companion Technical Supplement, *Transport route profiling qualification*.

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 successfully 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 requirement specification (URS). 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.

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

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.

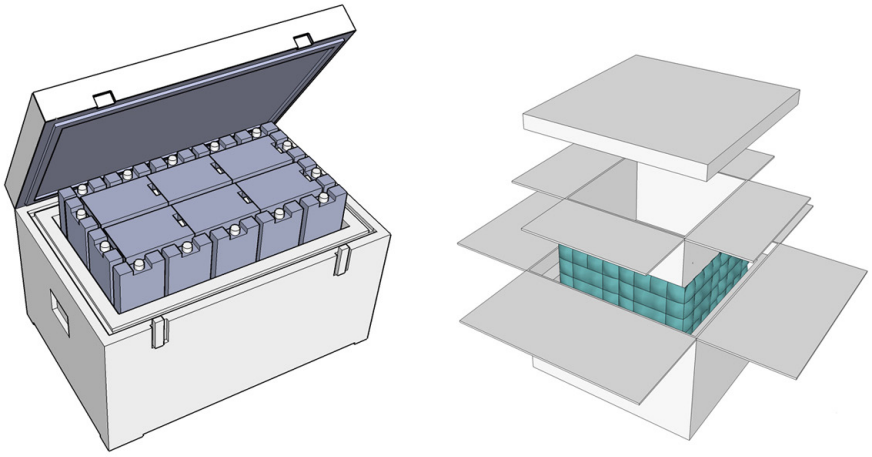
1.1 Requirements

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.

[5] The installation will typically incorporate components that have been design qualified.

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.

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

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.

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,

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

location of refrigerant, and refrigerant conditioning specifications. 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.

[9] See Technical Supplement: Transport route profiling qualification.

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.

[10] This could be a low-value "placebo" product chosen to reduce the risk of financial loss.

[11] See footnote 10 above.

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.

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.

o. 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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- American Society for Testing and Materials (ASTM) D3103; Standard test method for thermal insulation quality of packages. Conshohocken (PA): ASTM; 2014 (http://www.astm.org/Standards/D3103.htm).
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- International Safe Transit Association (ISTA) Standard 20; design and qualification of insulated shipping containers. East Lansing (MI): ISTA; 2014 (http://www.ista.org/pages/procedures/ista-standards.php, accessed 25 March 2015).
- 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).
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Revision history

Date	Change summary	Reason for change	Approved