QAS/14.598

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

August 2014

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Acknowledgments

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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

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[2].

Cool water-pack: A water-pack cooled to a temperature of +5.0°C before use[3].

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

Design qualification: 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)[4].

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

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[5].

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

[1] Source: WHO PQS
[2] Source: *ibid*
[3] Source: *ibid*
[4] WHO Technical Report Series, No. 961, 2011. *Annex 3: WHO good manufacturing practices for pharmaceutical products: main principles.*
[5] Source: WHO PQS

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 pre-conditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others.

Pharmaceutical product: Any product intended for human use or veterinary product intended for administration to food producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. Medical devices are not included[6].

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 pre-defined limits.

[6] 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 pre-defined environmental conditions and/or within pre-defined time limits, is degraded to the extent that it no longer performs as originally intended.

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

Validation: Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting pre-determined acceptance criteria.[7]

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[8].

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[9].

[7] PDA Technical Report No. 39: *Guidance for Temperature Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment*, 2007.
[8] Source: WHO PQS
[9] Source: *ibid*

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*[10].

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 drug 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 or performance qualification exercise involving shipping containers and refrigerated vehicles.

The 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.* Whilst 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[11] that has been assembled in a specific location is fully in accordance with the user requirements specification 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.*

[10] http://apps.who.int/medicinedocs/documents/s18683en/s18683en.pdf
[11] The installation will typically incorporate components that have a design 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.*

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 performance qualification 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 meet 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 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 vs. 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[12].

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[13].

[12] There are currently no recognized tools or references to help with this.
[13] Note that periodic monitoring is not a substitute for a formal route profiling qualification process.

2.1 Associated materials and equipment

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

- Electronic Data Logging Monitors (EDLM) 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 pre-programmed, 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[14], vented boxes are the most representative way to mimic this form of distribution and the unique handling and exposure which occurs there. 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. This should be written and 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 could be actual shipping destinations. Alternatively, select logistically similar locations which are better able to receive and return the EDLM's. 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, etc.

[14] The cubic size and weight of a package can make a significant difference in 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.

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. winter, summer, and other seasonal variability. This is to collect data that represents extreme temperature condition (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 sampling size:* ISTA recommends that at least 25 samples are applied 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[15] in case some of the test packages do not reach their intended destination or devices are not returned. This generally occurs to about 10% of the test shipments.

g. *Choose the study product:* Determine if 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 retrieval instructions and use of the shipping log. The user must be trained and know how to operate the EDLM's.

b. *Critical Control Points (CCP):* 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

[15] 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 there may be more than one monitored shipment on the vehicle in order to capture route profiling data for different drop-off points.

temperature controlled warehouse); this provides the information needed to link the temperature profile to specific events along the route[16].

c. *Placing data loggers*: In order to capture actual ambient temperature exposure, attach the EDLM on the outside of the shipper, or 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: tracking number; shipment date and time; shipping service level; destination, etc.

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 pre-paid 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 EDLM's 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;

[16] 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.

- Minimum temperatures;
- Maximum temperatures;

d. *Study errors.* The possibility exists that some data will not be included in the final analysis due to routine human error, device failure or other loss. A contingency plan should be defined for such events.
   - EDLM malfunction;
   - EDLM inadvertently not started / stopped;
   - Shipping information is not available for a data logger;
   - Loss of EDLM.

2.5 Understanding temperature exposure: the degree-hour concept

If a passive container, loaded with coolant and TTSPP product, 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 product 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 2.1 to 2.4 above. By analysing the collected data, the temperature exposure along different routes, or 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:

$$E = \sum(T \; x \; t_{dif})$$

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.

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[17]. 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 Table 1 example, Shipment E has received the greatest exposure and Shipment A, the least.

[17] 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.

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 pre-qualified cold boxes and vaccine carriers whose cold-life, cool-life and warm-life at constant ambient temperature have been tested and published[18].

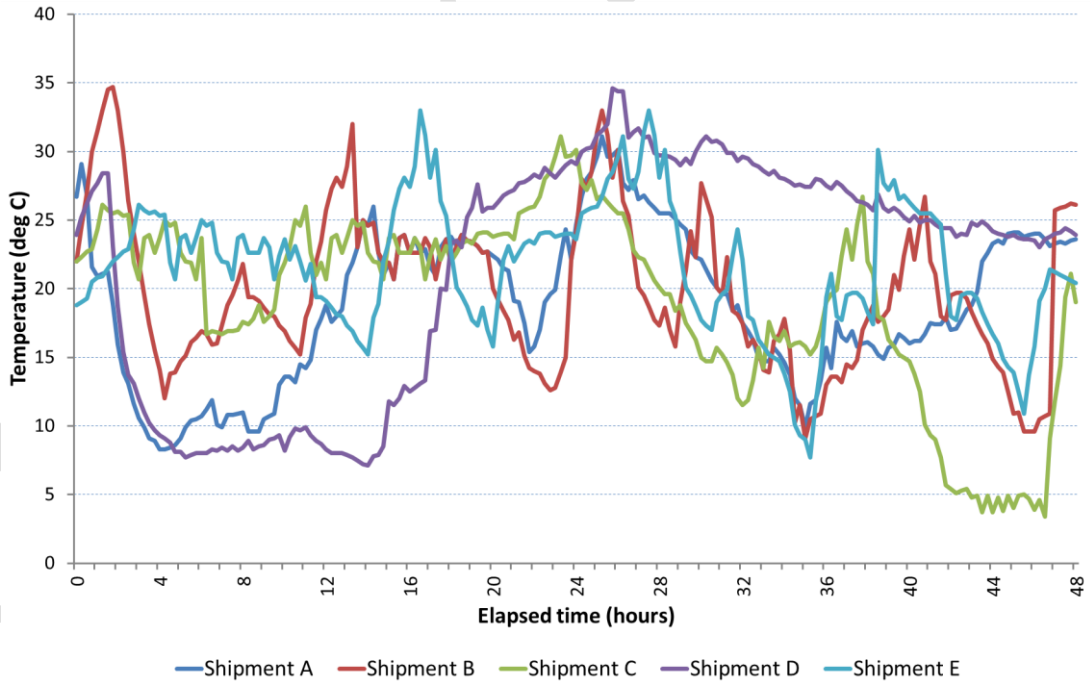
2.6.1 Method A for designing and testing packaging solutions

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 operational qualification 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 fewer than 30 trips are available for analysis, frequent periodic monitoring can be used to verify the results.

Figure 1 shows the Table 1 data 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:

[18] 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

- 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 it 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 (1,040 degree hours).
- Shipment E is actually the 'worst case' at 1,042 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 deceiving.

In order 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 four hour 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 2 – Superimposed step graph. Degree-hours = worst case

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[19].

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[20]:

- 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 cool-life 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.

[19] *ibid*

[20] The temperature thresholds given below are those used for the WHO PQS prequalification tests.

- 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.

$$E = \sum(h \, x \, t_{dif})$$

Where:

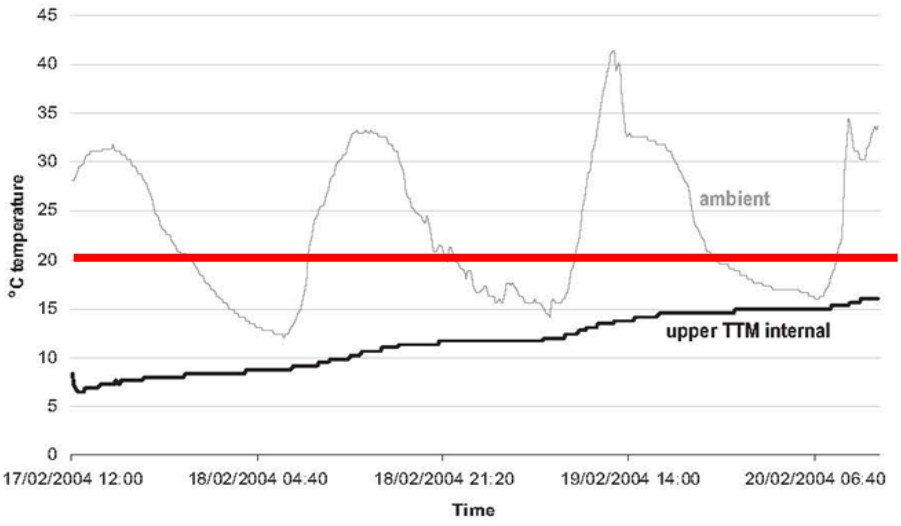
E = Total temperature exposure above the threshold temperature, in degree-hours.
h = Time increment above the threshold temperature, in hours.
t_{dif} = Temperature difference in °C between the threshold temperature and ambient for each increment.

The threshold temperature is selected on the following basis:

- For cool water-packs, the threshold must not exceed +20.0°C. A lower temperature (say +15.0°C) may be chosen if required.
- For frozen and conditioned ice-packs the threshold is normally +8.0°C.
- For warm water-packs, the threshold is normally 0.0°C.

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, U. 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 transport temperature of the TTSPP and a *cold climate* situation where the ambient temperature is consistently below the minimum recommended transport temperature 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.

References

- 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.* Parenteral Drug Association, 2007.
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- International Safe Transport Association (ISTA) Series 5B, 7E and Manual 20, *Design and Qualification of Insulated Shipping Containers.*
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Annex 1 – Method B examples

This Annex describes the Method B approach 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 over 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 A5.2 describes the calculation method for the warm climate case and section 5.3 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 at 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:
   $$E = SUMIF(first\ data\ point{:}\ last\ data\ point, \text{">threshold temperature"}, first\ data\ point{:}\ last\ data\ point) * logger\ interval\ in\ hours)$$
   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 A5.2.

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 three other profiles remained above the threshold 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 x 43 = 516 degree-hours.
b. 516 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 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:
   $E = SUMIF(first\ data\ point{:}\ last\ data\ point, "<\text{threshold temperature}", first\ data\ point{:}\ last\ data\ point) * logger\ interval\ in\ hours)$
   The column totals indicate the total temperature exposure for the separate shipments in degree-hours *below* the chosen threshold temperature and allows 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 if a proposed passive container has a long enough warm life 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 x -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