BEST PRACTICE ON TRANSPORT QUALIFICATION: GOOD DISTRIBUTION PRACTICE
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About BioPhorum

The BioPhorum Operations Group’s (BioPhorum’s) mission is to create environments where the global biopharmaceutical industry can collaborate and accelerate its rate of progress, for the benefit of all. Since its inception in 2004, BioPhorum has become the open and trusted environment where senior leaders of the biopharmaceutical industry come together to openly share and discuss the emerging trends and challenges facing their industry.

Growing from an end-user group in 2008, BioPhorum now comprises over 80 manufacturers and suppliers deploying their top 2,800 leaders and subject matter experts to work in seven focused Phorums, articulating the industry’s technology roadmap, defining the supply partner practices of the future, and developing and adopting best practices in drug substance, fill finish, process development and manufacturing IT. In each of these Phorums, BioPhorum facilitators bring leaders together to create future visions, mobilize teams of experts on the opportunities, create partnerships that enable change and provide the quickest route to implementation, so that the industry shares, learns and builds the best solutions together.
1.0 Executive summary

When qualifying shipping lanes or qualifying thermal protection systems (TPS) for transportation of temperature-controlled products, each pharmaceutical/biopharmaceutical company uses differing standards and processes, resulting in a lack of consistency across the industry. Correspondingly, vendors/suppliers of the transport equipment currently lack a common standard to include within their specific tests of, for example, active or passive shipping solutions for the pharmaceutical industry. However, because many regulatory bodies have differing requirements and guidance for transport qualifications, the necessity for a common standard approach to the level required—i.e. data, qualifications, standards, etc.—cannot be leveraged effectively.

Consequently, it would be beneficial for the industry to utilize a consistent process/approach for the qualification of both the equipment and shipping lanes, with clarity on the specific test requirements of each element, namely the operational qualification (OQ) and performance qualification (PQ). Harmonization across the industry would lead to significant benefits, in terms of a reduction in the time taken to perform transport qualifications, a decrease in resources required and repeated work, as well as a fewer number of required shipping solutions—all of which translate to substantial financial savings. Similarly, in order to adhere to the vast and scattered regulatory demands, collectively agreeing on one standard of performing transport qualifications may also substantiate the effort in pursuing the overarching objective, namely patient safety. Importantly, it is essential that the pharmaceutical/biopharmaceutical industry not only agrees on the latter but, at the same time, works closely together with vendors/suppliers and authorities/regulators to accomplish this.

This paper seeks to develop such a best practice (standard) to define elements of overall transport qualification principles. As such, a best practice proposal is presented in terms of how to perform the various types of qualifications in a highly regulated environment. Finally, the benefits for the industry of adopting such an approach are elaborated upon.

This paper is a joint work within the BioPhorum storage and transport collaboration.
2.0

Introduction

Temperature-controlled supply chain management is a highly dynamic and unpredictable process. Hence, ensuring supply from manufacturer to patient is no easy or trivial task to ensure. Temperature controlled vehicles (TCV), equipment and packaging materials present a variety of complex challenges from a regulatory compliance point of view. Additionally, today’s pharmaceutical manufacturers and their distribution providers must keep abreast of the latest solutions and technologies to guarantee the robustness of their supply chains. Finally, in a post-recession world, as of today, there is an even greater pressure around cost-containment. Thus, manufacturers face tough decisions when choosing the right solutions for their supply chain, specifically in terms of their trade-off between cost, compliance and service (the three legs of ensuring a cost-efficient compliant distribution set-up).

Traditionally, validation and/or qualification principles and concepts are related to good manufacturing practice (GMP) and aligned within the quality management system (QMS), which is designed based on manufacturing processes where an equipment or system is usually physically fixed to one location during the validation and where the environment surrounding the system is controllable. That is not the case for a transport system, which is dynamic in nature and, more specifically, has an external environment that is not easily controllable. Additionally, most pharmaceutical companies do not own any transportation equipment, meaning they have to ‘rely’ on global forwarding companies that contractually take over responsibility for the shipping of the products, i.e. in compliance with regulatory conditions by sea, air and road. However, most if not all regulatory agencies are of the opinion that regardless of transportation agreements and contracts with third party logistics suppliers, pharmaceutical companies are still responsible for ensuring safe delivery of products to patients.

This has led to various regulative definitions regarding the principles of transport qualifications and/or validations. Moreover, to secure compliance, industry-wide interpretations are designed where often the most rigid and strict regulative definition sets the bar. This paper therefore presents a set of new guiding principles for transport qualifications (TQ), based primarily on OQ and PQ from a pharmaceutical industry point of view.

2.1 Transport qualification — process

There is a tendency among the pharmaceutical manufacturing industry to believe that it is not possible to conduct transport validations. Transport is a highly dynamic (and uncertain) task, which is uncontrollable, as compared to, for instance, production environments. It is therefore creating an inaccurate picture of the process to use the term ‘validation’.

2.2 Transport and distribution — breaking the cold chain

Previously, there has been a widespread consensus among regulatory bodies and authorities that transportation is merely storage on wheels. However, the lack of availability of controls, and increase in complexity in distribution and transportation, mean that it is not currently practical to set the same expectations (for transportation) as with storage. Figure 1 on the next page illustrates a typically primary distribution flow.
The distribution chains in Figure 1 (respectively a sea and air corridor) point to the several potential ‘breaks’ (represented as the red circles) in the cold chain. Moreover, air transportation is not usually controlled (e.g. aircraft cargo holds are not typically temperature-controlled), the loading/unloading at sea ports necessitate unplugging the refrigeration unit of the reefer container and customs handling may need to open the TPS. This can apply during transit, where, for example, truck transport or airport warehouses may also be uncontrolled.

2.3 Requirements from authorities — process

Historically, less focus from authorities was put into transport qualification studies pertaining to pharmaceutical products. However, in recent years, regulatory bodies and agencies have placed more and more attention on distribution practices for pharmaceutical companies. Concurrently, this increased focus has led to the issuance of numerous regulations and guidelines by various health authorities among others with regards to qualification and validation of pharmaceutical transport systems and related processes. A small excerpt is presented in Figure 2.
Currently, pharmaceutical products stored at manufacturing sites have drawn huge attention with regards to maintaining or securing a controlled environment, i.e. in relation to temperature and associated stability of the drugs and its components. The transit and, hence, transportation of the product, whether it is finished product, bulk, medical devices, DS (drug substance) or API (active pharmaceutical ingredient) should obviously restrictively also undergo the same controlled environment. Transportation of these items has risk of temperature variation due to a variety of both internal and external factors, therefore it is necessary to control the whole transportation supply chain, equipment and processes.
3.0 Purpose and scope

The purpose of this document is to provide a set of general principles, minimum standards and specific guidance for the development and execution of, respectively, the operational qualification and performance qualification studies within the context of the overall transport qualification process, as presented in Figure 3.

Figure 3: Overall transport qualification process

An overarching risk-based process should be utilized—the risk-based qualification plan is not necessarily a specific document but the approach to take.

The design qualification (DQ) is the process of obtaining and documenting evidence that the TPS has been designed in accordance with user requirements.

The OQ is intended to document, through a formally approved test plan (protocol), that a TPS performs as intended under the anticipated shipping conditions in compliance with the user requirements and the manufacturer’s recommendation. The OQ consists of simulated transport tests under controlled conditions, which must be conducted in a qualified laboratory with calibrated equipment designed for the purposes of environmental testing and documented following good laboratory practices. Note, that for some active TPS, controlled conditions may not be possible and a justification for an alternate process can be identified. The OQ challenges the worst-case conditions, including minimum and maximum loads, duration, temperature extremes, etc. that are representative of the anticipated shipping conditions.

The PQ is documented verification that the TPS, package preparation and handling processes can perform effectively, based on the approved procedures and specifications. In other words, the PQ is used to assess actual/live shipment preparation and distribution processes. As such, the PQ differs from the OQ, which challenges the worst-case conditions including minimum and maximum loads, duration, temperature extremes, etc. Essentially, the OQ defines the conditions, lanes, seasons, product loads, etc. limitations of the qualification. The PQ cannot be used to expand the defined limitations of the OQ. Because the PQ environment is not controlled, the environment may not be sufficiently challenging to fully demonstrate that the TPS’s success should be expected.

The scope includes:
- Shipments through commercial distribution (movement off the shipper’s property)
- All product types and temperature ranges and transport modes

The scope excludes:
- TPS that were implemented prior to approval of a company’s OQ/PQ process definition do not require the new OQ/PQ outlined in this paper.
- Routine movement of materials with an owner’s property that are part of processing

Transition rules:
- Companies may not need to redo their qualification documents for existing shippers, this decision should be based on a risk assessment (the result will depend on how good/outdated the documents for existing shippers are)
4.0

Operational qualification (OQ)

The OQ can be completed by the manufacturer of the TPS and accepted by the user (e.g., pharmaceutical company) if the qualification meets the intended use environment. This may require the user to write a cover memo. If the manufacturer OQ cannot be fully leveraged, then additional testing may be required to support a robust OQ package that meets end-user requirements.

Upon the completion of the OQ, the acceptable parameters of the TPS will have been defined. These can bracket a variety of use conditions and may include:

- Minimum and/or maximum product payload (mass, volume and payload type)
- Minimum/maximum product temperatures. These may or may not match the storage temperature limits. Often referred to as the 'shipping temperature range' or 'allowable excursions', this is the temperature range, supported by stability and other studies, within which a product can be transported for a short duration of time without adverse effect on product quality
- Ambient temperature profiles covered (lanes, seasons)
- Duration. This is 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
- Orientation of the TPS during shipping
- Packout process requirements. This includes the correct placement of product, dunnage and refrigerants, the conditioning requirements for product and refrigerant (e.g., time and/or temperature), as well as any potential refrigerant replacement/refreshment en route, if applicable. Where beneficial, it can be considered to have separate OQ documents for different seasonal packout configurations of the same TPS and/or different models/sizes of a similarly designed TPS
- Location for the temperature monitoring device(s) to be used in routine shipments

The following are the OQ guiding principles:

- A risk assessment should be performed to consider the impact of variables in the transportation process other than those conditions that are continuously controlled or monitored, e.g., delays during transportation, power-off times at ports, failure of monitoring devices, replacement or refreshment of refrigerant, or other relevant factors. These variables are to be incorporated into the OQ. It is up to each company to determine how to incorporate this risk-assessment approach;
- Bracketing can be considered as part of the OQ testing. In its simplest form, bracketing can justify testing for multiple shipping lanes or payloads by using just a few worst-case configurations. The user requirements must specify the intended use. There is a balance between cost and a TPS qualified for the greatest flexibility;
- The use of a pre-approved protocol required with well-defined acceptance criteria;
- Separate from the OQ is the qualification of components. Approved components are to be used in the OQ. Qualification of the components may have been completed in an installation qualification (IQ). The expectation is that vendors will have justified that their IQ process is robust;
• Sound rationale to justify the test methods used and test parameters identified must be documented in the OQ protocol. Test methods may include recording interval of temperature monitors, etc.;
• If test failures and/or critical exceptions are identified during execution, an investigation must be performed and documented. The investigation must identify the most probable root cause(s) and assess impact to the qualification testing;
• A final report should document the test performance and compare the results with the acceptance criteria set out in the OQ protocol.

Specific principles for shock and vibration OQ:
• Physical OQ testing (shock and vibration) is required to prove the robustness of the TPS in the anticipated shipping environment.

Specific principles for thermal OQ:
• The thermal OQ testing is conducted using an ambient profile(s) that encompasses all the anticipated extremes for transportation mode and seasonal/locational temperatures for all intended shipping lanes over the duration of the transportation process:
  • Both hot and cold profiles should be used for each packout configuration unless justification is provided
  • The profile(s) should incorporate hot and cold environmental extremes that are representative of the lane(s)/route(s). However, these are not necessarily the hottest or coldest ever single temperature
• The thermal OQ testing challenges the conceivable/realistic worst-case conditions defined by parameters, which can include: minimum and/or maximum payload, location of refrigerant and refrigerant conditioning specifications (noting that, dependant on the scenario, not all of these parameters will have a worst case)
• Further, multiple temperature monitors and/or thermocouples will be used to identify temperature variability throughout the payload area, e.g. as presented in the PDA TR64 and ISTA Standard 20
• The thermal OQ testing will identify the appropriate location for temperature monitors during actual shipping
• Multiple tests are to be completed to demonstrate reproducibility
• If the intended use of the TPS would allow re-icing or opening of the TPS during shipment, this must be considered in the OQ
• Reusable shipping container systems, with and without interchangeable parts, should be qualified to ensure that the intended use, including thermal performance, has not been adversely affected as a result of age, physical damage or other failure modes

If substitutions or modifications to the design or packaging are made, an OQ must be carried out or additional scientific rationale to justify no additional testing. There may also be other reasons to justify the need for an OQ, such as changes to the process—for example, if the mode of transport and, thus, the surrounding ambient environment have changed.

There are two aspects of OQ testing of the TPS, condensed into shock and vibration and thermal testing.

4.1 Shock and vibration OQ
The shock and vibration testing should be evaluated for both active and passive thermal protection systems.

When considering shock and vibration testing, there are two components: 1) testing to prove the TPS can survive normal shipment; and 2) testing to prove the product payload is able to survive normal shipment. This paper will focus on the former: to challenge the robustness of the TPS and its ability to protect a payload. Shock and vibration testing for the product, primary packaging and secondary packaging is necessary, but out of scope of this paper.

Table 1 depicts the best practices for OQ shock and vibration testing of thermal containers.
The following is a detailed explanation of the recommended best practices detailed in Table 1 for OQ shock and vibration testing:

**Acceptance criteria**

**Definition:** predefined parameter(s) that must be met to successfully complete a test.

**Best practice:** assessment of the ability to maintain a defined temperature range post-test. This includes:
- Loss of integrity, e.g. broken refrigerant packs or broken insulation. This could be a visual test only, testing in a chamber is not required
- When the logger location is specified, maintenance of location is maintained
- Tamper evidence of the TPS is maintained (when specified)

**Justification:**
- It is necessary to prove that the TPS can perform as expected when exposed to the shock and vibration rigors of a distribution environment

**Simulated transport testing standard**

**Definition:** the simulated distribution testing protocol to be followed.

**Best practice:** recognized standard justified by the manufacturer, e.g. ISTA, ASTM, ISO.

**Justification:**
- It is recommended that simulated distribution testing is completed as it is reproducible and repeatable
- The manufacturer should identify the appropriate industry standard that is representative of the planned use environment (e.g. parcel testing vs palletized load testing) and payload (maximum mass)/package to be tested
- Alternately, the manufacturer may have defined a custom test series that must be justified as representative of its intended use

### Table 1: Operational qualification shock and vibration testing best practices

<table>
<thead>
<tr>
<th>Item #</th>
<th>Test – shock and vibration</th>
<th>Best practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acceptance criteria</td>
<td>Assessment of the ability to maintain a defined temperature range post-test, additionally:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Loss of integrity, e.g. broken refrigerant packs or broken insulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• When the logger location is specified, maintenance of location is maintained</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tamper evidence of the TPS is maintained (when specified)</td>
</tr>
<tr>
<td>2</td>
<td>Simulated transport testing standard</td>
<td>Recognized standard (when applicable) justified by whoever is doing the testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>e.g. ISTA, ASTM, ISO</td>
</tr>
<tr>
<td>3</td>
<td>Payload</td>
<td>Maximum mass</td>
</tr>
<tr>
<td>4</td>
<td>Number of tests</td>
<td>Minimum of one test, three separate containers is recommended</td>
</tr>
<tr>
<td>5</td>
<td>Test day post-packout (conditioning time)</td>
<td>Justify when in duration of packout to execute the simulated distribution test, based on the types and combinations of refrigerants you have</td>
</tr>
</tbody>
</table>
Payload
Definition: the load carried by a TPS (e.g. product), exclusive of what is necessary for its operation (e.g. refrigerant).
Best practice: to utilize the maximum allowable payload mass.
Justification:
- The maximum allowable mass is recommended. This will provide the upper limit of mass that will be allowed to ship in this container.

Number of tests
Definition: the number of TPS required to consider the OQ complete.
Best practice: minimum of one test is required per packout, i.e. one TPS. However, three tests are recommended for added assurance (they can be the same or separate containers, based on the output of risk assessment).
Justification:
- Any requirements in the chosen standard should be followed
- Additional testing is not required but recommended to increase the chance of finding a defect or differences due to variability in the container, refrigerant or packout
- ISTA recommends one test
- Shock and vibration is less complex compared to thermal OQ testing (where three tests are required), i.e. it is simple drop testing versus thermal testing with sensors that have inherent tolerances for data

Test day post-packout (conditioning time)
Definition: the recommended conditioning time post-TPS packout and prior to the start of simulated distribution testing.
Best practice: the manufacturer to justify when in duration of packout to execute the simulated distribution test.
Justification:
- There may be multiple considerations to determine how long to condition the TPS post-packout and prior to testing. For example:
  - The chosen distribution standard may have a requirement (e.g. ISTA 3A is 12 hours)
- Consider physical state of the refrigerant:
  - The refrigerant may move (e.g. frozen refrigerant as it thaws) or sublimate (e.g. dry ice) as time passes
  - When could the refrigerant impart the most damage to the payload
- The manufacturer must justify when in the duration of the packout is worst case for testing for shock and vibration
4.2 Thermal testing OQ for active and passive systems

The thermal OQ should be completed with both active and passive thermal protection systems. Due to the differences in how the systems function to maintain temperature, two tables have been provided to outline best practices. Tables 2 and 3 present the best practices for OQ thermal testing of an active system and a passive system respectively.

Table 2: Operational qualification thermal testing best practices for active system

<table>
<thead>
<tr>
<th>Item #</th>
<th>Test – OQ active</th>
<th>Best practice</th>
</tr>
</thead>
</table>
| 1      | Payload         | • Minimum and/or maximum load considering mass and volume, which is reflective of the worst-case condition(s) following a load assessment  
          • In most situations, this worst case would be minimum mass with maximum volume  
          • All payload must follow TPS loading instructions (e.g. proximity to air vent, use of pallets, strapping) |
| 2      | Ambient test profile | Representative of shipping route(s) containing all realistically anticipated worst-case extremes |
| 3      | Duration |
|        | When under direct power (plugged in):  
          • 24 hours minimum, enough to capture defrost periods  
          • For active systems under battery power  
          • Minimum requirement: test to the defined duration (acceptance criteria)  
          • Recommendation: test beyond the acceptance criteria  
          For active systems when there is no power (battery or plug in):  
          • Minimum requirement: test to the defined duration (acceptance criteria)  
          • Recommendation: test beyond the acceptance criteria |
| 4      | Thermal container orientation | Consider alternate orientations when the total weight (TPS and payload) is below 70kg  
          Test upright only above 70kg |
| 5      | Loading and unloading times | Representative of the process at both the sending and receiving sites (e.g. door open durations, preconditioning of the active system, the product, etc.) |
| 6      | Temperature probe mapping and location | Map the payload area to identify hot and cold spots  
          Consider rationale for either testing in the simulated product (i.e. within the primary packaging or next to (outside primary packaging) the simulated product |
| 7      | Temperature probe routine location | Identify routine location(s) for data logger(s) |
| 8      | Recording intervals | Between 1 and 15 minutes |
| 9      | Number of tests | 3 under direct power  
          Plus other testing for battery power and no power |
The following provides a detailed explanation and justification of the points depicted in Tables 2 and 3, as well as a rationale, variations and possible considerations of nuances. Where applicable, the explanation and justification is separated for passive and active shipments. Where this is not stated, the explanation and justification applies to both.

**Payload**

**Definition:** this is defined as the contents, product or simulated product within a TPS.

**Best practice:** minimum thermal mass with maximum volume.

**Justification:** minimum thermal mass with maximum volume is classified as worst case since increased thermal mass will increase the temperature stability, so minimal thermal mass will decrease the temperature stability. In addition, the larger occupied volume in a TPS is also worst case since it can disrupt airflow.

**Assumptions:** maximum volume equates to maximum cargo volume within the TPS, which fills the entire payload space.

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**Ambient test profile**

**Definition:** the time and temperature for each node of transit, which can include, but is not limited to, nodes such as storage, cargo build, tarmac exposure, flight, etc.

**Best practice:**

- Passive systems: representative of ambient profile(s) that encompasses all the anticipated extreme routes in terms of time and temperature, which includes a hot and cold profile
- Active systems: as per passive. In addition, profile can be representative of a continuous worst-case soak at a specified temperature representative of hot and cold seasonal extremes

**Justification:**

- Passive systems: worst-case time and temperature should be included within the ambient test profile for hot and cold seasonal extremes to ensure the contents within the TPS are capable of maintaining the temperature acceptance criteria to provide assurance during routine shipments
- Active systems: reference minimum durations section against worst-case soaks, which is sufficient to test the performance of the system since these systems use compressor-driven technology. Testing against other profiles of varying temperature will challenge other aspects of the active system (e.g. programming of thermostatic controls). However, under worst-case soak this will be biggest drain on the systems battery

**Assumptions:** for active systems (i.e. reefers or TCVs) it is assumed that in certain cases the ambient profiles can be representative of real-world worst-case mapping due to the size constraints of the TPS.

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### Table 3: Operational qualification thermal testing best practices for passive system

<table>
<thead>
<tr>
<th>Item #</th>
<th>Test – OQ passive</th>
<th>Best practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Payload</td>
<td>Minimum and/or maximum load considering mass and volume, which is reflective of the worst-case condition(s) following a load assessment. In most situations, this worst case would be minimum mass with maximum volume.</td>
</tr>
<tr>
<td>2</td>
<td>Ambient test profile</td>
<td>Representative of shipping route(s) containing all realistically anticipated worst-case extremes</td>
</tr>
<tr>
<td>3</td>
<td>Duration</td>
<td>Minimum requirement: test to the defined duration (acceptance criteria) Recommendation: test beyond the acceptance criteria by a minimum of 5%</td>
</tr>
<tr>
<td>4</td>
<td>Orientation</td>
<td>Consider alternate orientations when the total weight (TPS and payload) is below 70kg Test upright only above 70kg</td>
</tr>
<tr>
<td>5</td>
<td>Packout/unpack process</td>
<td>Representative of the process at both the sending and receiving sites (e.g. temperature of packout area, time to assemble the container, packout time, any in transit holds in refrigerated or frozen conditions, preconditioning of the refrigerant/dunnage/data logger, the product, etc.)</td>
</tr>
<tr>
<td>6</td>
<td>Temperature probe mapping and location</td>
<td>Map the payload area to identify hot and cold spots Consider rationale for testing in the simulated product vs next to the simulated product</td>
</tr>
<tr>
<td>7</td>
<td>Temperature probe routine location</td>
<td>Identify routine location(s) for data logger(s)</td>
</tr>
<tr>
<td>8</td>
<td>Recording intervals</td>
<td>Between 1 and 15 minutes (WHO ref)</td>
</tr>
<tr>
<td>9</td>
<td>Number of tests</td>
<td>3 per packout configuration with the worst-case configuration (e.g. payload, ambient profile etc.)</td>
</tr>
</tbody>
</table>
Duration

Definition: this is defined as the period of time to demonstrate performance of the TPS against the ambient test profiles.

Best practice:
- Active (direct power): a minimum of 24 hours against each ambient test profile, inclusive of defrost cycles
- Active (battery or no power) and passive: predefined duration equivalent to worst-case shipping route duration as specified in the acceptance criteria—ensuring testing beyond acceptance criteria by a minimum of 5%, but until failure of acceptance criteria is preferable. This allows for expanded understanding of performance past acceptance criteria limit

Justification:
- Active (direct power): a minimum of 24 hours is recommended since, during this time, the container would have been subjected to various conditions such as compressor cycling and defrost modes
- Active (battery or no power) and passive: predefined duration equivalent to worst-case shipping route duration is recommended to ensure performance of the TPS against representative actual shipping route durations within the network. Testing beyond the acceptance criteria at a minimum of 5% provides additional data on the TPS to justify use, in the event delays occur during actual shipments within the network

Assumptions: acceptance criteria is representative of the worst-case shipping route duration.

Thermal container orientation:

Definition: this is defined as the physical positioning of the TPS as either X, Y or Z-axis during thermal testing within the chambers.

Best practice:
- For TPS + payload less than 70kg, consider alternate orientations during thermal testing besides the Z-axis (i.e. X and Y axes) similar to distribution testing (vibration and drop testing) orientations for small parcels, which is representative of transportation in three axes
- For TPS + payload greater than 70 kgs, the recommended thermal testing positioning is Z-axis, which is representative of the typical axis during transport

Justification: small parcels travel through transportation networks in all orientations (X, Y and Z-axis), which should be considered during thermal testing to ensure there is no effect on the TPS to maintain temperatures. Freight (unitized loads) travel through a transportation network in the Z-axis where it is handled in the upright orientation with mechanical equipment (i.e. pallet jacks and forklifts). Therefore, a single orientation (Z-axis) can be considered during thermal testing.

Assumptions: this strategy assumes that although ‘small parcel’ means less than 70kg, any package between 35kg and 70kg defaults to being at a weight heavy enough to use mechanical equipment for movement. Also, TPS + payload that is less than 35kg but contains a mini-pallet would default to moving up to the freight category.
Packout/unpack process

**Definition:** In shipping studies, a packout typically refers to an insulated container or shipping system that uses a refrigerant to keep the payload area (and, consequently, product within this area) within a specified temperature range for a specified duration during shipping. Sizes range from parcel to pallet and multi-pallet systems. They typically do not have active temperature control capability. Refrigerants may be gel packs, dry ice or phase change materials. The packout configuration follows a defined methodology. This methodology (in the form of instructions for configuration) is similar to a specification document and is considered as an input for thermal qualification of the packout system.

**Best practice:**

- It is best practice to perform a risk assessment of the shipping process prior to initiating any thermal qualification studies on a packout. (It is up to each company to determine how to incorporate this risk-assessment approach)
- During qualification, all packout components (including temperature data loggers) and quantities must be specified and documented
- At a minimum, creation of the packout must be performed with draft procedures or instructions
- The packout process must be documented at the time of configuration
- Pre-conditioning requirements for all packout components must also be documented
- Checks and balances must be in place for verification of preconditioning requirements of the packaging components
- The process for packout configuration (environmental conditions and duration) must be accounted for during qualification and should reflect worst-case operations at the sending site
- The process for packout receipt (environmental conditions and duration) and payload retrieval and storage must be accounted for during qualification and should reflect routine operations at the receiving site
- When refrigerant replenishment is required, this should be accounted for within the OQ protocol

**Justification:**

- Critical considerations for thermal qualification of the packout are thermal mass, conditioning and type of the refrigerants, worst-case shipping durations and exterior ambient temperature
- The qualification approach should incorporate worst-case considerations for thermal mass. Thus, a minimum load is typically used for testing

**Assumptions:** Where refrigerant replenishment is necessary, robust quality agreements must be in place and relied on to ensure expectations for quality assurance are met.
Temperature probes: probe placement for thermal mapping and for routine shipping operations

Definition: a temperature probe in this context refers to the temperature data loggers or sensors used during shipping-related thermal qualification studies. Thermal OQ studies of passive systems involve traditional thermal mapping of the payload area. This is done by placing multiple temperature data loggers or sensors at strategic locations in the payload area to measure ambient temperature within the payload area.

Best practice:

- The choice of temperature probe or sensor during thermal OQ studies is dependent on the study design. Considerations include the need for real-time temperature data monitoring during qualification, measurement accuracy specifications, temperature ranges and the types of data loggers to be used for routine monitoring. Reporting and alarming capability of temperature data loggers is another important consideration;
- Size of the payload area is a factor in determining the number of sensors to use for thermal mapping. Pallet or multi-pallet shippers will require several sensors due to the size of the payload area. Best practice for temperature logger placement during mapping studies is, at a minimum, to place sensors in the corners and geometric center of the payload area within the TPS. For smaller parcel shippers it is not unusual to utilize no more than two sensors in the payload area during thermal qualification;
- It is important to monitor exterior ambient temperatures (during shipping-related thermal qualification studies), since the ability of the shipping system’s payload area to maintain temperature is dependent on exterior ambient temperatures. This is to be able to demonstrate that the environmental chamber was able to properly simulate the desired profile;
- Product thermal behavior may be monitored (by placement of a temperature probe in the surrogate product) as part of the qualification study. This is dependent on the study design;
- Where the TPS has a fixed temperature probe installed (for example, a large active container, e.g. vehicle or sea-freight containers) that data can be considered for information purposes only.

Justification: It is best practice to design the qualification study to determine the best location for placement of a data logger if one is to be used for routine shipments; Another consideration for temperature logger placement for routine shipments is a location that allows easy and ready retrieval, to ensure that data loggers are always retrieved after shipments where this is part of the shipping process.

Assumptions: calibration is a minimum requirement for all equipment (including temperature data loggers) that requires calibration and is used in qualification studies for GDP purposes. Calibration is performed using a recognized and traceable standard.
**Temperature probe routine location**

**Definition:** Identify routine location(s) for data logger(s).

**Best Practice:** These may or may not be the same as the temperature mapping location.

**Justification:** For routine shipments, depending on the risk assessment and the acceptable level of risk, a decision may be made to include temperature data loggers with all shipments to enable monitoring during shipping.

**Recording intervals**

**Definition:** Recording or measurement intervals refer to the interval at which temperature data is logged by the temperature data logger or temperature sensor during a qualification study.

**Best practice:** Between one and 15 minutes.

**Justification:**
- The choice of sampling rate should be at the appropriate resolution to allow conclusions to be drawn from any anticipated qualification events. For instance, where it is applicable for open-door recovery studies to be performed, the resolution of data should be sufficient to allow for analysis of the performance of the payload area during the open-door test;
- The sampling interval should also be based on the expected length or duration of the thermal qualification test. The choice should not be such that an overwhelming amount of data is collected with minimal benefit or impact to the study conclusions;
- Intervals used for routine shipments should be based on the type of data logger and memory requirements and expected duration of shipments;
- For routine shipments, data loggers with alarming capability may be used. Alarming schemes usually involve calculations that are based on the measurement intervals.

**Assumptions:** N/A.

**Number of tests**

**Definition:** In line with qualification/validation principles, a certain number of replicate tests need to be performed to demonstrate that the shipping system will consistently perform as expected.

**Best practice:**
- It is typical to evaluate the performance of the shipper’s payload area against a worst-case hot season ambient temperature profile;
- It is typical to evaluate the performance of the shipper’s payload area against a worst-case cold season ambient temperature profile;
- A minimum of three replicate tests is required (they can be the same or separate containers, based on the output of risk assessment).

**Justification:** The risk assessment is an input into the choice and quantity of tests required. For instance, cold seasonal extreme profile challenge tests may not be necessary for frozen shipments. Due to variability and complexity within thermal testing, three replicates are required to add sufficient confidence in the results.

**Assumptions:** N/A.

Essentially, the best practice suggested in Tables 1, 2 and 3 delivers evidence and guidelines for TPS manufacturers to perform OQ tests that biopharmaceutical manufacturers are then able to leverage the tests within their standard operating procedures. Where TPS solutions are similar to those where sufficient testing has already been provided, there are cases where it can be justified that no or limited OQ testing can be sufficient.
5.0 Performance qualification (PQ)

The performance qualification (PQ) of a specific TPS is the documented verification that the TPS, package preparation and handling processes can perform effectively based on the approved procedures and specifications (PDA TR 39). The PQ differs from the OQ, which challenges the worst-case conditions including minimum and maximum loads, duration, temperature extremes, etc.

The following are the PQ guiding principles:

- Pre-approved protocol required with well-defined acceptance criteria
- A successful PQ will meet the acceptance criteria
- Sound rationale to justify the test methods and variables used must be documented in the protocol
- Variables include product, load size, lanes, etc.
- ‘Approved procedures’ include the OQ and/or site procedures and/or receiving site procedures, if applicable, and/or corporate global guidance and/or detailed procedures within the PQ protocol
- Bracketing approach (multiple shipping/receiving site(s), transportation service providers, etc.) can be used if justified—PQ can be leveraged in multiple routes as long as the specified process is followed in every route
- A shipper may have multiple configurations (e.g. seasonal)—a PQ should be performed for each configuration unless justified
- PQ is to be executed by trained personnel
- Vendor data to replace or reduce the testing requirements for PQ may be acceptable when justified and if testing is performed according to this document’s guidance:
  - Consideration must be made to address risks related to the ability of the shipping and receiving sites and transportation service provider(s) to properly condition, assemble and handle the TPS as applicable
  - Assumptions of what the OQ has established (as defined in the tables 1, 2 and 3):
    - Reproducibility
    - Appropriate location for temperature monitors during actual shipping
    - Minimum and maximum product load (mass, volume)
    - Products covered
    - Ambient temperature profiles covered, seasonal variations, high and low temperature extremes
    - Duration
- Temperature monitoring:
  - Routine or periodic temperature monitoring of the TPS provides an ongoing performance confirmation. Monitoring of each shipment limits the shippers risk while periodic monitoring allows the shipper to accept a level of risk from gaps between assessments
  - Monitoring of each TPS or a periodic assessment using temperature monitors must be defined in an approved procedure. When periodic monitoring is prescribed, the rationale for frequency and timing must be justified
  - It is recommended to utilize calibrated electronic temperature monitoring during PQ testing
  - Electronic monitors that are downloaded and offer the ability to assess the temperatures throughout the shipment provide additional visibility into the shipment performance and assist in deviation evaluation
- Reusable TPS
  - For a reusable TPS, a PQ is not necessary for individual TPS (e.g. temperature-controlled trailers, active ULD (unit load device)) if a PQ has been executed for a representative TPS or fleet
  - Not every unit needs to be qualified
  - Reusability aspects are covered under the OQ, not under a PQ
  - Reusability aspects include topics such as number of uses, maintenance, refurbishments, cleaning, etc.
Based on the guiding principles set out above, Table 4 sets out best practice for performance qualification.

<table>
<thead>
<tr>
<th>Item #</th>
<th>Test — PQ</th>
<th>Best practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td># of runs</td>
<td>min 1</td>
</tr>
<tr>
<td>2</td>
<td># of routes</td>
<td>min 1, appropriate to scope of qualification</td>
</tr>
<tr>
<td>3</td>
<td>Seasons</td>
<td>Not required (robust and included in OQ)</td>
</tr>
<tr>
<td>4</td>
<td>Materials</td>
<td>Representative of product (or empty where appropriate)</td>
</tr>
<tr>
<td>5</td>
<td>Acceptance criteria</td>
<td>Temperature, damage, duration (depending on DQ and OQ)</td>
</tr>
<tr>
<td>6</td>
<td>Number of routine loggers per unit and location</td>
<td>1/unit minimum, located as defined in OQ</td>
</tr>
<tr>
<td></td>
<td>External loggers (outside)</td>
<td>Not mandatory, if used, data is for information purposes; recommended</td>
</tr>
</tbody>
</table>

The following provides a detailed explanation and justification to the five points depicted in Table 4, as well as a rationale, variations and possible considerations of nuances:

**Number of runs and routes**

**Best practice:** a minimum of one PQ shipment (i.e. run) is required (which can cover single or multiple routes, depending on the scope of the PQ).

**Justification:**

- Many variables in distribution are generally out of the control of the shipper (e.g. external temperature, weather delays, transport equipment and personnel at different points of distribution, etc.) and multiple parties are in control of the shipment during distribution (freight forwarders, ground handlers, ramp agents, port longshoreman, etc.);
- Because these variables are relatively fluid (may vary from shipment to shipment) and difficult or impossible to control, a number of runs that is statistically justified is similarly challenging to develop. With this in mind, a single shipment is expected to be representative of any typical shipment, and sufficient to meet PQ expectations, to assess typical performance of the TPS in the field;
- The OQ challenges the expected extremes along all of the routes covered by the scope of the qualification;
- Reproducibility against worst-case conditions is demonstrated in the OQ. The OQ defines the worst-case conditions that are qualified, while actual field conditions are expected to be within the limits of the OQ:
  - Significant variables: some variables have traditionally been considered significant for worst-case testing; however, since the PQ is not intended to reflect a worst-case condition, these do not need to be included in PQ testing. These include variables such as weekday vs weekend shipments, etc.
- Routine monitoring of shipping also provides a verification of performance and reproducibility;
- If multiple shipping sites and/or receiving sites are in the scope of a PQ, not all sites may need to participate in the execution of a shipment based on risk assessment.
Seasons

**Best practice:** execution of the PQ runs during seasonal time periods is not required unless the configuration is designed for a specific season (e.g. summer configuration is to be tested in the summer season).

**Justification:** the PQ’s purpose is not to test the combination of TPS and route in extreme conditions (e.g. product loading, external temperatures, duration, etc.). Extreme conditions are considered during OQ testing.

Materials and payload

**Materials best practice:** actual or representative product loads, including empty loads, may be used that are within the parameters defined in the OQ.

**Payload best practice:** a quantity of material that is representative of typical shipments or a quantity representing a challenge to performance.

**Justification:**
- Worst-case conditions do not need to be met by the representative material(s) because the OQ challenges the extreme conditions;
- Actual product can, but does not need to be used, as long as a justified representative product(s) is used as payload. A material is to be considered representative if it has similar material properties (e.g. density, thermal mass) as the product(s) it represents;
- No product load (an empty TPS) may also be used in the PQ as long as minimum mass, maximum volume was defined in the OQ:
  - For a TPS qualified with no product load, utilizing the largest empty box that will fit the usable space within the TPS is considered a worst-case condition. This is because, from a thermal mass perspective, utilizing the least amount of thermal mass provides the greatest challenge to the TPS maintaining desired temperatures (thermal mass, when introduced into the TPS within its desired temperature range, will limit temperature variability); from a volume perspective, limiting airflow within a container (especially when utilizing active TPS) with the largest volume possible will challenge natural and forced convection, which will lead to the highest level of temperature stratification within a TPS (more uneven temperatures within the TPS volume).

Acceptance criteria

**Best practice:** the PQ acceptance criteria is to include the following requirements:

- **Temperature:** temperature requirements matching those defined in the OQ, including allowable excursions are to be maintained during transportation;
- **Physical damage:** gross visible damage (as per typical site/receiver standard receiving procedure) should not occur:
  - This applies to the TPS only if no product or other materials were used in PQ
  - Otherwise this applies to the TPS and product or other materials used in the PQ
- **Shipment duration and process:** shipment duration and transportation process should follow the planned transport lane duration and process:
  - Shipment duration and process (e.g. transport mode, etc.) should be similar to the anticipated duration and process; deviations are to be documented and justified
  - At times the intended process cannot be followed due to unexpected circumstances (e.g. extreme weather, mechanical failure, etc). If the transportation service provider/s (TSP) follow their procedures to manage these circumstances, a deviation is not required, but this should be discussed in the PQ report
  - If a shipment takes place in a significantly shorter duration than expected (e.g. as per OQ duration), this is acceptable if the shipment process expected was followed;
- **Results that are better than expected** (e.g. longer in duration, and/or tighter in temperature control, etc.), would not increase the allowable or expected performance of the TPS since this needs to be addressed in the OQ.
Justification:

- PQ is intended to provide evidence that the performance of a TPS on a representative route will result in appropriate temperature control and physical protection. Product and process requirements are to be verified upon receipt to assure this is the case:
  - The requirements provided address the primary areas of concern during distribution of biopharmaceutical products, temperature and physical damage
  - Additionally, shipment duration and process assures that the expected process that was expected to be followed took place at a high level
  - Shipment arrival prior to the limit of duration need not be held until the full, qualified duration is reached
  - Deviations to expected duration may be accepted if all standard operating procedures (SOPs) were followed and resulted in meeting the temperature and damage criteria
  - Shipments arriving late may be used to evaluate the TPS and close the PQ if determination is documented that the handling was not representative of typical handling and that procedures are in place to routinely arrive within the qualified duration
  - Inspection for physical damage should be at the outer most levels of packaging typical of the receiving process, i.e. for full pallet shipments to a wholesaler, inspection of the TPS and/or the pallet outer packaging (stretchwrap, etc.) and/or the shipping case
  - Destructive inspection is not required (e.g. opening of cartons or cases that would destroy tamper-evident seals, etc.)

Temperature monitoring

Number of loggers per unit and location best practice: a minimum of one calibrated temperature monitor is to be placed within the payload of the TPS; the quantity and location is to match normal operations as defined in OQ:

External loggers (outside of TPS) best practice: the use of external loggers is optional but recommended.

Justification:

- The PQ is intended to be representative of a typical shipment
- The quantity and location of monitors to be used during normal operations is justified based on the OQ:
  - Temperature monitors inside shipping cases or other internal locations as well as product probes are not required unless this is the normal operation
- The ambient temperatures are not part of the acceptance criteria; consequently, collecting the ambient temperature is not mandatory. Failure to capture ambient temperatures during a PQ shipment does not constitute a failed shipment or require an additional shipment
- Collection of ambient temperatures can provide confirmation that the route conditions were within the range of the OQ
6.0

Discussion and suggestions for future set-up

As presented in this paper, specific considerations must be made following the guiding principles. Importantly, the OQ pertaining to the shipper module/equipment must render conceivable/realistic ‘worst-case’ considerations, albeit presenting a feasible/potential deviating event. With that, temperature and time must fulfill the initial acceptance criteria, both in terms of the TPS and operation, as to specific time and ambient temperature exposure on the lane.

The PQ, on the other hand, is and should be simpler in scale. This qualification approach must render proof to the initial OQ onto whether the real-life shipment is within the limits presented in the OQ. It is not suggested to map a PQ to a specific product or product-specific requirement, as inherited from the definitions—a PQ is to support the shipper and/or lane set-up. A failure is, therefore, related all the way back to the shipper module—for instance, if a failure occurs due to long customs release in a PQ, then it would most likely not be the shipper that fails but the process or the assumptions of what the process was supposed to be.

Qualifying a (new) lane with an existing TPS, where an OQ for the equipment exists (i.e. for a trailer, shipper box, pallet shipper, etc.) does not need a supplementary OQ performed. Accordingly, this should be reflected when and if a PQ fails, i.e. failure to meet the acceptance criteria must be investigated to determine root cause; note, if the causes identified can be classified as non-routine changes to the TPS or the process may not be required. For example, mishandling resulting in a forklift truck puncture may allow an additional PQ shipment under the same protocol or other corrective action. Otherwise, if failure results of a PQ require a change to the TPS, this would also require a requalification of the TPS through OQ; or if a failure result of a PQ requires a change to the process, this will require a separate PQ and may require a separate OQ.
7.0

Concluding remarks

Pharmaceutical manufacturers for whom transport and distribution of medicinal products requires storage under a controlled temperature should use the guidelines and approaches presented in this document to evaluate and limit temperature-excursion risks to these products.

Recommendations pertaining to the proposed OQ/PQ process in this paper represent industry consensus and have the goal of protecting the product while minimizing risks of unsupported temperature excursions.
# Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceptance criteria</td>
<td>predefined set of conditions that must be met for the PQ to be considered successful</td>
</tr>
<tr>
<td>External loggers (outside of TPS)</td>
<td>the number of temperature monitors to be used outside each TPS to establish the temperature of the environment (e.g. ambient temperatures)</td>
</tr>
<tr>
<td>Freight forwarder</td>
<td>a freight forwarder, forwarder or forwarding agent, also known as a non-vessel operating common carrier (NVOCC), is a person or company that organizes shipments for individuals or corporations to transport goods from the manufacturer or producer to a market, customer or final point of distribution</td>
</tr>
<tr>
<td>Ground handler</td>
<td>in aviation, aircraft ground handling defines the servicing of an aircraft while it is on the ground and (usually) parked at a terminal gate of an airport</td>
</tr>
<tr>
<td>Longshoreman</td>
<td>a person employed in a port to load and unload ships</td>
</tr>
<tr>
<td>Materials</td>
<td>the type of contents within the shipping TPS during the execution of PQ (e.g. payload)</td>
</tr>
<tr>
<td>Number of routes</td>
<td>the minimum number of unique routes determined to be sufficient to qualify a distribution region containing multiple routes in scope of the PQ</td>
</tr>
<tr>
<td>Number of routine loggers per unit</td>
<td>the number of temperature monitors to be used within each TPS to establish the temperature of the payload/materials</td>
</tr>
<tr>
<td>Number of runs</td>
<td>the minimum number of unique shipments executed as part of the PQ. A unique shipment is comprised of an individual shipping system (e.g. TPS) utilized in a route (see definition below)</td>
</tr>
<tr>
<td>Payload</td>
<td>the amount of material to be utilized during execution of the PQ</td>
</tr>
<tr>
<td>Ramp agent</td>
<td>airport personnel marshaling aircraft, loading/unloading and sorting freight and baggage, servicing the aircraft, assisting with pushback and towing, de-icing and other duties as assigned</td>
</tr>
<tr>
<td>Route (i.e. transit lane, transport lane)</td>
<td>a unique shipping route as defined by a unique set of predefined variables. This must include, at minimum, the origin and destination. The route may be defined narrowly to apply to a unique origin, destination and shipping nodes, or may be defined broadly, independent of shipping nodes (transfer points or stopovers at airports, hubs, ocean ports, etc.). Variables within the OQ must address the attributes of the defined transit lane</td>
</tr>
<tr>
<td>Seasons</td>
<td>refers to the execution of the PQ runs during seasonal time periods (e.g. winter, spring, summer, fall)</td>
</tr>
<tr>
<td>TPS</td>
<td>entire system and configuration(s)</td>
</tr>
</tbody>
</table>
References


Health Canada, Guidelines for Temperature Control of Drug Products During Storage and Transportation (GUI-0069), (October 2005)


ISTA Standard 20 Revision 2, Test Standard 7E, (2010)

ISTA Procedure 3A: Packaged-Products for Parcel Delivery System Shipments 70kg (150lb) or Less (standard, small, flat or elongated), (2018)

PDA – Parenteral Drug Association, Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products Through the Transportation Environment, Report no. 39, Bethesda (MD), 2007


USP – United States Pharmacopeial Convention, General Chapter <1079> Good Storage and Shipping Practices, USP convention no. 28, Suppl. 2, (August 2005)

