Model for Qualification of Shipping Systems for Temperature Sensitive Pharma Products

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Abstract

Rising expectations in Good Distribution Practice (GDP) are highlighting a need for having a transparent and process driven supply chain comprising of transport systems, shipping lanes and equipment qualified to meet the product and patient needs. In these circumstances, pharmaceutical supply chains have developed models addressing these requirements and ensuring product and patient safety throughout the supply chain. Shippers of pharma products are also expecting that Logistics Service Providers (LSPs) have designed Quality and Risk Management Systems (QRMS) in place to respond to these requirements by providing lane risk assessments (LRAs). This article evaluates logistics industry capabilities and compliance level in distribution risk assessments and provides a model for the Qualification of Shipping Systems used in transport of temperature sensitive pharmaceutical products by road, air, ocean and rail.

Keywords

Shipping system, lane risk assessment, qualified equipment, qualified shipping system, GDP, compliance, vehicle, LSP, qualification

Glossary

CCP – Critical Control Points

CSV – Computer System Validation

DC – Distribution Centre

DQ – Design Qualification

GDP – Good Distribution Practices

IQ – Installation Qualification

KPI – Key Performance Indicator

LRA – Lane Risk Assessment

LSP – Logistics Service Provider

OQ – Operation Qualification

PQ – Performance Qualification

QRMS – Quality and Risk Management System

QSS – Qualified Shipping System

SC – Supply Chain

SOP – Standard Operating Procedure

Introduction

Temperature sensitive pharmaceutical products should be transported under temperature-controlled conditions in order to maintain product quality using a Qualified Shipping System (QSS). For the purpose of this article, such system is defined as follows:

- A Qualified Shipping System is a defined transport process that consists of a qualified vehicle and/or equipment (e.g. active and/or passive transport system) with payload that is moved from origin to destination (shipping lane) via planned transit node(s) using qualified transport mode(s) (e.g. road, air, ocean, and/or rail) and qualified logistics service providers (LSP) under known seasonal conditions, time constraints and risks.

One of the key stakeholders in distribution is the LSP, who should have a QRMS built on defined and qualified processes according to the Good Distribution Practices (GDP) systems. Today pharma shippers are selecting LSPs based on their GDP compliance capabilities and systems that includes trained employees, compliant processes, subcontracting systems, computer system validation (CSV), data integrity, but also ability to conduct a thorough risk assessment on services they are offering. This requirement comes in focus nowadays since the GDP can no longer be limited to efforts in avoiding temperature excursions or delays, or even split shipments.

Regulators and pharma industry do not have one common understanding laid down in a single standard or guidance on requirements and expectations related to qualifications in transport of temperature sensitive pharma products. For example, some regulators are demanding that each shipper of (bio)pharmaceutical products qualify their shipping lanes and/or systems[1], while others are less restrictive. In addition, different terms are used across guidelines. Table 1 summarizes some key wordings related to qualification requirements[2].

Table 1: References to qualification requirements

Reference	Key Wording
WHO Technical Report Series, No.961, Annex 9, 2011.	Qualify active and passive shipping systems.
USP General Chapter 1079.	Seasonal temperature mapping.
EU GMP, Annex 15: Qualification and Validation.	Transportation routes should be clearly defined. Risk assessment should be performed to consider the impact of variables in the transportation process.
APIC – Active Pharmaceutical Ingredients Committee. GDP for API.	The ability of the contract acceptor to comply with these requirements should be evaluated.
ANVISA, Guidance on the Qualification of Transportation of Biological Product, 12th of April 2017.	The main purpose of the qualification is to show the robustness of the transportation systems used. The transportation system qualification cornerstones are the performance qualification and operation qualification of the system to be used for the transportation of the biological products.

Establishing a Qualified Shipping System

A system is an organized and structured set of elements (see Figure 1) combined with functional purpose, to transform input requirements in an output respectful of the system purpose and design. In order to qualify a Shipping System for a product, a minimum of five elements

should be assessed as a set of GDP and transport Critical Control Points (CCP):

1. **Product** is the first element to be assessed by the shipper and includes, but not limited to the allowable temperature shipping conditions, shipping destination and, type, size and weight of packaging.
2. **Pre-qualified LSP** is a predisposition in a Qualified Shipping System. The LSP is responsible for adequate transport mode(s), shipping equipment and transport lane selection based on conducted risk analysis and risk mitigation. As such, the LSP should develop and maintain a QRMS compliant to GDP. The verification of their level of compliance is done through due diligence audits. The Quality Agreement between the shipper and the LSP defines and documents their roles and responsibilities.
3. **Supply Chain Capabilities** is the next element that is documented in a Lane Risk Assessment (LRA) including a documented risk identification, analysis and evaluation on shipping system elements such as transport mode, particularly lane, transit node, time constraints and type of qualified equipment planned for use in distribution. The documented LRAs are offered by LSPs as their standard service and part of their QRMS. The LRA for a particular lane will show the level of risks connected with each CCP of the transport process and proposed actions (risk mitigations) to reduce or eliminate the risk. Documented LRAs support pharma shippers in making a decision on the type of shipping vehicle and/or equipment; active or passive to be used depending on the products characteristics and potential product and process impacts.
4. **Pre-qualified Shipping Vehicle and/or Equipment** is used to protect the product integrity throughout the supply chain. Typically shipping vehicles and/or equipment is divided in two groups; active or passive transport equipment. The active transport equipment uses an actively powered system which uses electricity or other type of power to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic control (e.g. active air container, ocean reefer container etc.)[3]. Passive transport equipment[4] is a closure or a component assembly designed to protect the product to a limited time when exposed to different seasonal conditions. Capabilities of such systems in respect of intended use are defined in the manufacturer's DQ, IQ and OQ documentation, using some sort of cooling agent such as cold packs of gel, water, dry ice or phase change materials having ability to keep the refrigeration for a limited, predefined duration.
5. **Quality Risk Control Strategy** is the final element that addresses all actions to be taken in order to minimize transport risk such as temperature excursions and damage, and to maintain product quality based on the product, pre-qualified LSP, supply chain capabilities (e.g. mode of transport, transit time, shipping lane, LRA) and pre-qualified shipping vehicle and/or equipment. Depending on the change, the outcome can be to update SOP's, provide training, execute Performance Qualification (PQ), continuous temperature verification and/or risk-based temperature monitoring. PQ is a higher level of qualification than the LRA and it is typically conducted on the selected "worst case" lane defined based on risk assessment. PQ provides evidence that the selected mode(s) of transport (e.g. road, air, ocean and/or rail), shipping vehicle and/or equipment maintain the product quality. A PQ will confirm documented OQ of the pre-qualified shipping vehicle and/or equipment, documented LRA and defined distribution SOP are followed on all CCPs of the process.

Figure 1 shows a graphical display of the five elements that determine the Qualified Shipping System. In the following paragraphs supply chain capabilities, pre-qualification of shipping vehicles and/or equipment and quality risk control strategies are further explored.

Figure 1: Elements of a Qualified Shipping System

Supply Chain Capabilities

The pre-qualified LSP should describe in the LRA the supply chain capabilities compared to requested service transport requirements. The LSP should provide the risks and integrity of their shipping vehicle/equipment including, for example, insulated boxes for last miles delivery including transport and planning of the duration of passive packaging, quantity of cooling material and other logistics components. The temperature profiling of each lane should be established to enable the shipper to evaluate potential level of risk to the service [4, 11].

The engagement of the LSPs in PQ studies is typically limited to provision of documented LRA for a particular transport as a backbone for any qualification and PQ transport runs execution. Typically, LRAs are not used in OQ - ASTM simulations done by the shippers but follow a predefined risk matrix provided by international standards. However, LRA's can provide valuable information about the shipment duration and seasonal temperature variability as time and

temperature are critical process parameters during the OQ of thermal packouts.

Part of the standard LRA delivered by the LSPs is use of passive or active equipment. Different manufacturers have developed similar types of active containers in air freight operating on the same principles, but following their own requirements. On the other hand, ocean reefer containers are designed and built based on ISO standard 1496-2 and compliance to ATP and ATO standards. Review and acceptance of transport equipment qualification documentation (DQ, IQ, OQ and/or PQ) performed by the equipment manufacturer should be considered as good industry practice since re-qualification by the pharma manufacturers would not add value to already conducted systematic qualifications. Shippers however should be offered a documented risk assessment on the intended use, i.e. an LRA for a lane using a particular type/model of transport equipment and thus confirming its suitability for the intended use. Types and models of transport equipment such as active containers in air freight and ocean reefer containers are manufactured by different companies. As long as analysis can show the installed components and operational characteristics are the same, the interchangeability should apply thus enabling shippers to utilize the same type of equipment delivered by different manufacturers in cases where the originally planned type of equipment is unavailable. This is important at those times of year where a potential lack of such equipment on the market could occur caused by popular demand.

An LRA on air and ocean freight for example focuses on SC capabilities only, evaluating risks related to:

- port handling time and operations (e.g. unplug time of ocean reefer container, tarmac time at airport etc.)
- temperature-controlled storage capabilities
- capacities at origin, transit and destination
- fleet capabilities
- shipment duration and variability
- alternative origin, transit or destination ports
- capacity constraints and so on

Detailed SC capability risk assessments are focused on process related risks and do not account for product impact risks. In other words, the documented LRA as delivered today by the LSPs does not encompass evaluation of the SC risks on the particular product being transported but on the defined transport temperature service range like +15°C to +25°C or +2°C to +8°C being two standard air freight transport ranges[5]. Argument might be this is neither the intent of this systematic risk analysis nor a responsibility of the LSP. The LSP is required to maintain defined transport temperature service range through defined shipping process having no or limited knowledge on product characteristics or capabilities to withstand standard shipping conditions. Ultimately, the shipper is responsible for selection of the shipping system (active or passive) knowing the impact level to product based on the designed transport process. Accepting this premise, question rises on how useful are these types of documented LRAs in overall risk evaluation for the product being distributed [3, 5, 6, 12].

Evaluating SC capabilities goes in line with service offered by the LSP. Having a door to door coverage is often, if not in all cases, a question of network capabilities, incoterms and the LSP network. In such cases the service offered would go as far as the airport gateway in certain markets or the ocean port of entry thus leaving the last CCP segment to local brokers or other, locally engaged LSPs responsible for bringing the product to the consignee. In some cases, if the LSP does not operate their own branch office in the market, the General Sales Agent can be present under contractual relation with the LSP selected. Incoterms are presenting another challenge in this segment, particularly when contractual manufacturers are concerned. More remote or long-distance markets are challenges by themselves where additional risks are identified in operational schedules and available capacities.

Delivery of detailed and comprehensive SC capabilities analysis with indication of associated risks and proposals for their mitigation is thus an important part of any qualification and a solid start in risk analysis for the product distribution but also insufficient. Here what is needed is shown in Figure 1. The product impact evaluation and risks are not evaluated in LRAs done by LSP, but only the process and service risks.

Pre-Qualification of Shipping Vehicle/Equipment

Shipping vehicle equipment should be qualified for the intended use[7,8] to ensure temperature integrity and security of the product during the entire distribution process. To ensure vehicles and/or equipment used for transport is suitable for the purpose, an appropriate level of qualification or risk assessment as a minimum is required[2]. Different transport vehicle and equipment types will have different user requirements[7, 9] and qualification or temperature mapping models. For example, temperature-controlled road vehicles[7] should be temperature mapped to ensure hot and cold spots are identified. Records and results of temperature mapping studies on road trailers shall be maintained by the LSP and verified during the pre-contract audit. Where practical, aircraft cargo compartments can be temperature mapped and results accounted for in a risk assessment to determine a level of exposure to environmental conditions during transport. Temperature-controlled containers like active unit loading devices in air freight or ocean reefer containers should be subjected to all four levels of qualification; Design (DQ), Installation (IQ), Operational (OQ) and Performance Qualification (PQ)[9]. Where such up-to-date qualification documentation exists, the risk assessment is required to confirm suitability of the equipment to intended use.

Quality Risk Control Strategy

Qualification is defined as documented testing that demonstrates with a high degree of assurance that specific process will meet its pre-determined acceptance criteria[3].

Qualifications in transport and logistics are occasionally confused with validation thus two references to help understanding only

process, transport equipment or shipping systems qualifications are feasible[1,10].

Operational qualification (OQ) or laboratory transport simulation tests or "static" transport simulation studies are performed by specialized, qualified and approved testing laboratories. For transport simulations (OQ) the number of involved stakeholders in testing itself is typically minimized to the shipper and the testing lab contractual agreement although the applicable standard risk matrix for the simulation foresees different stakeholders' involvement thus indicating potentially higher risks. Typically, this refers to expectation of multiple handling and manipulation processes but also "change of hands" between different vendors with theoretically speaking, different levels of GDP compliance. OQ tests performed by the manufacturers primarily test the product packaging abilities and attributes such as temperature, humidity, shock and vibration.

According to PDA Technical Report 64[3] an Operational Qualification is "Documented verification that equipment or systems, as installed or modified, perform as intended throughout anticipated operating ranges." From the shipper standpoint, the OQs could be typically conducted during the product development phase where different types of packaging are subjected to laboratory tests using industry recognized international standards like ASTM or ISTA. During these tests primary, secondary and tertiary packaging is subjected to adverse conditions simulating worse case transport conditions the product could encounter in the supply chain. Often in international shipping this type of packaging would be further packed in additional outer packaging or consolidated on a logistics pallet as a main distribution unit. In such cases consolidation to a higher logistics unit (passive for example) further reduces risks to which the shipper box for instance, was subjected during the ASTM test.

PDA Technical Report 64[3] also provides a definition of PQ as "Documented verification that the equipment and ancillary systems, when connected, can perform actively and reproducibly based on the approved process method and specifications." Here, referring to equipment, the same paradigm can be applied on a process, i.e. shipping process or a shipping system. Thus, the OQ would still remain transport simulation testing according to relevant standard and PQ a real-life transport of product in a defined shipping lane for which the LRA is typically documented prior to the PQ runs execution.

A question for further discussion is the worthiness of PQ runs as seasonal real-life shipment transports since those are highly dependent on current and future capacities over the lane or even operational frequencies. For example, a particular lane from an air and/or sea port in Europe to a country in Latin America can be qualified during PQ runs only to end with limited capacities available thus placing constraint in regular supply. In addition, carriers of active air containers and ocean reefer containers can change overnight or on short notice transport nodes due to strikes and/or natural disasters for example. A business contingency plan should address such potential risks but not all outcomes of dynamic logistics environment can be foreseen besides the fact the real-life PQ runs are costly. This might lead to conclusion that "worst case" (distance in mileage, longest transit time) lane PQ seasonal runs are supporting as a representative model for all other lane PQ runs in the network. Another challenge may be found in regulatory authorities' interpretations. For the new product launches real life PQ runs might be a part of the filing thus making it a prerequisite for the particular market. In these circumstances, deviations from the original lane for which the PQ runs were performed should be handled through a change control process based on risk assessment. In cases where a different product is shipped using the same transport temperature range and temperature monitoring location(s), previous transport shipping system qualification should be considered applicable as long as the same or similar lane, LSP and/or carrier are used in the same transport mode. The shipping system for +2°C to+8°C products to a particular market once qualified should be considered valid for all other products using the same transport conditions, lane, LSP and carrier thus enabling manufacturer to utilize from the previous work on seasonal "worst case" PQ runs as long as continuous temperature verification is executed at hot/cold spot(s) as defined in the OQ. A risk analysis would still be required on intended use to confirm applicability of already qualified lanes – shipping systems. Some regulatory agencies like Brazilian ANVISA, state a clear expectation on conducting three seasonal PQ runs required for biological products[1] and maintain supply over the qualified lane. Such specific requirements if interpreted literally, could lead to supply challenges for a particular market in cases where those lanes cannot be used due to force majeure like natural disasters, industrial actions or geo-political uncertainties.

Model for Qualified Shipping System

In order to establish and maintain a Qualified Shipping System solution, a model is proposed that consists of seven steps based on the synthesis between PDA Technical reports 39, 58, 64 and 72, ICH Q9 and GDP guidance. From initiation of the change to performance monitoring, deviation handling and continuous improvement, the system offers optimized process with all system control measures required in today's regulatory environment (see Figure 2):

1. Initiate change for new product, shipping vehicle/ equipment, transport mode, LSP and/or lane.
2. Initiate Quality Risk Assessment for new product, shipping vehicle/equipment, LSP and/or lane in order to determine risks and requirements based on historical, actual, future and/or simulated data.
3. Lane Risk Assessment by LSP on CCPs, capabilities and services at origin, transit nodes, destination, use of transport modes and active/passive equipment.
4. DQ/OQ on shipping vehicle/equipment executed with product, dummy or placebo in a controlled test environment (e.g. lab, climate chamber) using anticipated temperature and shipping duration profile per winter/summer season. The OQ tests performed by the equipment manufacturer are acceptable as long as it includes simulated payload.

Figure 2: Qualified Shipping System

1	2	3	4	5	6	7
Initiate **Change** for new product, shipping vehicle, transport, mode, LSP and/or lane.	**Quality Risk Assessment** for new product, shipping vehicle/equipment, transport mode, LSP and/or lane in order to determine risk and requirements based on historical, actual, future and/or simulated data.	**Lane Risk Assessment** by LSP on supply chain capabilities and services at origin, transport nodes, destination, use of transport modes.	**DQ/OQ** on shipping vehicle/equipment executed with product, dummy or placebo in controlled test environment (lab, climate chamber) using anticipated temperature and shipping duration profile per winter/ summer.	**Quality Risk Control Strategy** by implementing/ updating SOPs, contracts, training, and maintenance. Adjust requirements if needed.	**PQ, continuous verification and temperature monitoring** of Shipping System with product, dummy or placebo in shipping vehicle from origin to destination using selected transport mode(s) by LSP.	**Quality Risk Review** of deviations, complaints, audit observations and trends (KPI). Initiate change/CAPA if needed.

5. Quality Risk Control Strategy by implementing/updating SOPs, contracts, training, and maintenance. Adjust requirements if needed.
6. PQ, continuous verification and temperature monitoring of shipping system with product in shipping vehicle/equipment from origin to destination using selected transport mode(s) by LSP.
7. Quality Risk Review of deviations, complaints, audit observations and trends (KPI). Initiate change/CAPA if needed.

Steps 1 to 4 are the input for the Quality Risk Control Strategy, which will determine whether an update of the shipping system is necessary and if a PQ should be executed before the first real life shipments with product. The Quality Risk Control Strategy will also determine how temperature monitoring of the Quality Shipping Systems must be executed to provide evidence that product quality is maintained during transportation. Market specific regulatory requirements are followed respectfully. The last step is essential for continuous improvement of the Qualified Shipping System and this may lead to a change and to start the sequence of steps from the beginning.

Conclusion

Qualification of Shipping Systems is a growing regulatory requirement towards shippers of pharmaceutical products. Industry requires clear understanding of these requirements and an aligned approach towards authority's expectations. Pharmaceutical shippers are using standardized types of tests during packaging design testing which should be further utilized for future transport simulations. Shipper boxes or pallet configuration transport simulation test could be combined with primary and secondary packaging test thus foreseeing future qualification requirements in supply chain. When same shipping system is used to distribute product under the same temperature range requirements, the previously conducted PQ runs should be taken in consideration as sufficient as long as there is supporting data (DQ, IQ, OQ) and risk assessment on intended use. In other words when a new product is being introduced having same transport requirements, an existing PQ data shall be evaluated to confirm no new studies are needed. This particularly refers to PQ runs conducted on designed "worst case" lanes. In PQ real life studies, previously performed ASTM transport simulation tests could be used to support void of additional post shipping study product impact laboratory testing.

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The mention of a product or service provider does not mean it is the sole product or service that is available for use.

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