Transport Risk Assessment and Verification – from Theory to Practice

Legal and regulatory requirements, including GMP and GDP guidelines, require that medicinal products should be stored and transported in a way that the delivered product maintains its quality and integrity and remains within the legal supply chain during storage and/or transportation. Storage and transport need to be described in the Pharmaceutical Quality System and the principles of quality risk management should be used for designing and managing these activities.

While the respective requirements appear to be well implemented for storage facilities in the pharmaceutical industry and the supply chain, observations in audits and inspections as well as frequent questions concerning transport requirements demonstrate that consultancy on this topic is highly valued.

The following discussion is based on the requirements described in the EU Guidelines on Good Distribution Practice of medicinal products for human use; however, the GDP Guidelines for active substances, the GMP Guidelines and similar regulations contain comparable requirements for the respective areas within or outside of the EU.

Transport as “Mobile Storage”
Transport is nowadays often referred to as “mobile storage”. However, compared to storage in warehouses, there are many more external factors that may affect product quality during transport, including, but not limited to:

- environmental factors (climatic zones, temperature, humidity, light, vibration...)
- mode of transport (air, sea, road)
- delivery routes
- transport duration
- number of transits
- holding times
- vehicles
- shipping containers
- transport temperature
- equipment to control environmental requirements (active, passive)
- equipment to measure environmental factors
- handling at airport
- handling at customs clearance
- security aspects (e.g. damage, contamination, adulteration, theft)

Chapter 9 of the EU GDP guidelines point out that it must be be demonstrated that the medicinal products have not been exposed to conditions that may compromise their quality and integrity during transport. The GDP guidelines explicitly request a transport risk assessment focusing on the temperature during transport as a critical factor for all medicinal products. The outcome of the risk assessment should facilitate decision-making where temperature controls have to be implemented. However, depending on the product, other factors (e.g. moisture, light, vibration, air pressure) may be considered critical for a specific product and should then be included in the risk assessment and be controlled or monitored during transport.

During this step, a grouping of products with comparable product characteristics, stability and delivery routes and/or the determination of a few worst-case scenarios may reduce the number and complexity of risk assessments to be performed.

During further steps, the transport mapping can be finetuned with additional information, e.g. on vehicle types, intermediate hubs, further transits, holding times, information on environmental factors, already established controls or monitoring of environmental factors, more detailed timelines, etc. (see list above).

Risk Assessment
Based on this more detailed transport mapping, a risk assessment can now be performed. A commonly used tool is the FMEA-analysis (failure mode and effect analysis). This method correlates the severity of potential failures with the probability of occurrence and the probability of detection and a resulting quantifiable relative risk score can be derived. However, other risk assessment tools can be used as an alternative (see, for example, ICH Guideline Q9).

Where transport routes are complex, it may be helpful to break them down and analyse the respective parts step by step.

Risk Mitigation/Minimisation Measures
After risk analysis and evaluation, risk mitigation or minimisation measures should be derived, where appropriate. The most effective and safe transport is usually the most direct and quickest one with the least number of transits. Questions to be considered for risk minimisation could therefore include the following: Is it possible to reduce transport time and/or holding times? Can the number and duration of transits be reduced (e.g. change of transport mode, change of vehicles, interim storage, etc.)?
reloading)? Can the shipping containers be improved? Do additional temperature controls (or other controls) need to be implemented? Thus, a risk assessment can also be used for the purpose of transport optimisation.

When risk minimisation measures meet their limits, it has to be decided whether the remaining risks are or are not acceptable (including the resulting consequences). The risk assessment and its results need to be documented and communicated. After a defined period, the effectiveness of the implemented measures should be controlled.

Transport Verification

It will obviously be impossible to perform a transport validation for entire delivery routes based on the outcome of the risk assessment(s), as a validation requires precisely replicable flows and parameters, and in transport too many variables are usually involved. However, a feasible alternative approach is a transport verification that can be performed in a structured way.

As mentioned above, temperature is a significant risk factor that can affect product quality. Thus, with the focus on the temperature, a transport verification process should confirm in a pre-defined scenario, based on the outcome of the risk assessment, that the products remain within a predefined temperature range during transport. This can be done by evaluating temperature records from accompanying data loggers, temperature indicators or similar while using qualified vehicles, transport equipment and calibrated temperature measuring systems. Additional controls of other relevant factors can be managed analogously, depending on the product characteristics and requirements.

The transport verification process should be described in a pre-defined transport verification protocol and assessed and concluded in a respective report, confirming the suitability of the defined transport routes. Seasonal variations have to be taken into consideration; thus, a predefined winter and summer scenario should be evaluated. However, as stated in Annex 15, due to the variable conditions expected during transportation, successful transport verification does not replace continuous monitoring and recording of any critical environmental conditions to which the product may be subjected, unless otherwise justified.

Outsourcing of Transporting Activities

Transport activities for medicinal products are often outsourced to carriers. The requirements mentioned in chapter 7 of the EU GDP Guidelines apply for outsourcing of such GDP activities. In Europe, carriers involved in transport of medicinal products neither hold a Wholesale Distribution Authorisation or GDP certificate (despite the fact that they also perform storage activities), nor are they controlled by the Competent Authorities. However, they have to comply with the requirements of the EU-GDP Guidelines. This should be taken into account for carrier qualification and re-qualification and subsequent carrier management.

Conclusion

Profound knowledge of the medicinal products concerned and the delivery routes are needed to execute risk assessments on transport. The risk assessment is a powerful tool for the planning of new transport routes, for optimising and controlling existing transport routes, and as the basis for subsequent transport verification.

REFERENCES