VAISALA / APPLICATION NOTE

COLD CHAIN COMPLIANCE

Qualifying Cold Chains, Writing Performance Qualifications and the Parenteral Drug Association Technical Report 39 (revised 27)

This application note gives a brief overview of the Parenteral Drug Association's technical report 39. After the overview of TR39, we use the guidelines described in the report to provide several best practices for writing a performance qualification protocol.

The PDA's TR39 was created in 2005 and revised in 2007 to harmonise it with EU regulatory expectations with the objective of providing "…guidance to industry on the essential principles and practices of transporting temperature-sensitive medicinal products through the transportation environment." It has become a widely used reference for best practices in qualifying cold chain processes.

The report is very much rooted in the Center for Drug Evaluation & Research (CDER) "Guideline on General Principles of Process Validation "and suggests that the principles of that guideline can be employed to qualify, as much as possible, multiple points in a temperature-controlled supply chain.

Although based upon the principles of validation, TR39 allows that a supply chain cannot be "validated" in the accepted sense of the word. The title of the report includes "Medicinal products," but this is further defined in the introduction by the term temperature-controlled pharmaceuticals (TCP); the report further qualifies the type of products that, where applicable, may be covered in the recommended temperature-controlled transportation processes:

- Investigational medicinal products
- Intermediates
- Excipients
- Active pharmaceutical ingredients (APIs)
- Diagnostic products

The TR39's guidance aligns with the Center for Drug Evaluation & Research (CDER) "Guideline on General Principles of Process Validation "and suggests that the principles can be employed to qualify parts of a supply chain. Those areas where the principles are not necessarily applicable, a change control process is used instead. The report distinguishes the process flow of the temperature-controlled supply chain into three areas:

- Identification of Requirements
- Development
- Implementation

The Development section of the process flow is where the necessary documentation for adherence to standards or regulations is determined and process validation principles are evoked to perform design qualification, operating qualification, and a performance qualification, wherever feasible and based on any risks that may have been identified in the identification steps.

As an example of the effectiveness of the TR39 process flow, let's look at a Form 483 excerpt to see where the observed deviation might have been avoided. This is excerpted from 483 issued to a US-based human cell and tissue HCT/p provider:

> *"On X/XX/200X, region X received three [units] from another…region; products had been in transit greater than 24 hours, which exceeded the validated shipping time of the container…"*

There are several possible causes of such a delay; even with a well-defined and documented transportation process flow, unforeseen events occur (e.g. weather, traffic, delayed border passage). Nor are the development process steps necessarily lacking because, according to the 483, the transport container has been validated for shipping duration. Part of the issue may be that the units have not been quarantined appropriately to ensure against their use.

This may be a failure in the implementation process; a failure to create a deviation management system that includes CAPA. Or, if the quality system includes deviation management protocols, the issue may be a failure to train staff in corrective and preventive actions, as well as how to implement, document and store those data. If training is not the issue, simply assigning responsibility for execution of CAPA processes might be the cause of this deviation.

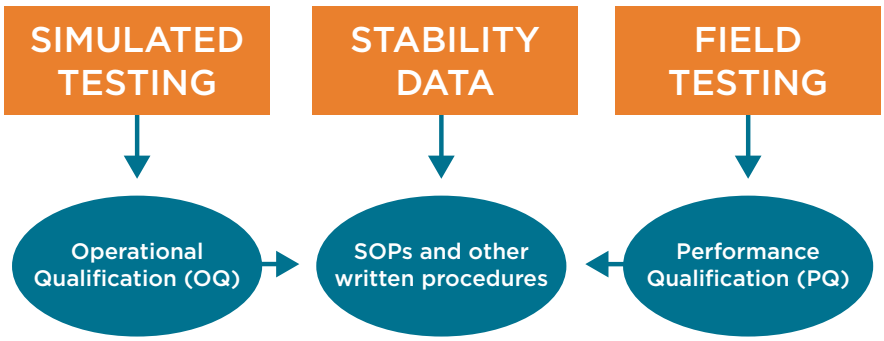
The 483 above refers to the need to not only have a validated supply chain wherever possible in order to satisfy regulators, but to also have a deviation management system that is understood and consistently executed by staff who are aware of their responsibilities.

Qualification Processes in TR39

As part of the Development section of its Process Flow recommendations, TR 39 outlines and lists minimum requirements for several processes for qualifying critical points of the temperature-controlled supply chain, including:

- Process to Qualify Protective Packaging
- Operational Qualification (OQ) – simulated testing
- Performance Qualification (PQ) – field testing
- Training
- Quality Systems that contain:
  - SOPs and other written procedures
  - Calibration program for instrumentation
  - Stability & OQ/PQ data
  - Deviation/Investigation reporting processes
  - CAPA program
  - Ongoing monitoring and reassessment
  - Change control program

The goal of this quality systems approach is to use data from several sources to anticipate the effect of temperature excursions during transport and create planned responses to ensure that adulterated product does not progress through the supply chain. The report outlines long-term and accelerated stability studies, temperature-excursion studies, and/or temperature cycling studies to predict the impact of temperature excursions on product quality during the transportation process.



Performance Qualification – Writing a protocol

Now that we've looked briefly at the PDA's technical report 39, you may be wondering how to create a protocol to qualify your cold chain. As in all qualification protocols, yours will contain different elements depending on the products and processes involved. However, a basic process validation protocol can serve as a guideline. Writing a protocol can seem daunting, but as in all carefully considered writing, describing the circumstances that surround the activity is key.

A good starting place for determining the content of protocol documents is the seven circumstances of classical rhetoric analyses specifically:

Quis, quid, quando, ubi, cur, quem ad modum, quibus adminiculis

These are: who, what, when, where, why, in what way, and by what means. We would also include a "What next?" circumstance, which can conclude your protocol with a section identifying the criteria for revalidation.

Conclusion

Supply chains that handle regulated temperature-sensitive products must not only transport goods from the manufacturer to the consumer, they must deliver products that will function as expected by the end user. The PDA, ISPE and similar organizations offer guidance in methods and procedures that are aligned with and based on state and federal regulations for pharmaceuticals, medical devices, biotechnology and other regulated products. Using the standards and guidelines of these organizations can help you ensure that the fundamental requirements of a regulated supply chain are satisfied.

For more information on cold chain applications, validation or monitoring, contact your local Vaisala representative, accessible here: **vaisala.com/lifescience**

SEVEN CIRCUMSTANCES FOR QUALIFICATION PROTOCOL ANALYSES

What:

- Identify the products to be transported and/or stored and include any specifications that relate to the product.
- The transport process that you are validating.
- The circumstances of "where" comprise the geographic path, including each point of transition (i.e. borders, climates, change of transport mode, change of service provider).
- Considering the points above -- the identification of product, processes, and pathways -- what are your criteria for a successful qualification?

When?

- Date(s) for completion and the length and duration of the validation.
- How often do you requalify your supply chain, or at least, your links in it?
- Are seasonal qualifications necessary?

Who?

- The operators and their qualifications and training.
- What personnel will be directly involved in the validation?
- What roles/job functions must be directly or indirectly involved?

How & By What Means?

- Describe the transport or storage process.
- Identify the utilities and or equipment to be used and include specifications and calibration/qualification information.
- Do you have any special controls during the qualification?
- State your statistical methods for data collection and analysis.

Why & In What Way?

- State the product parameters that are to be controlled and monitored.
- What product characteristics must be maintained and for how long? (IE: Controlled Room Temperature)

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