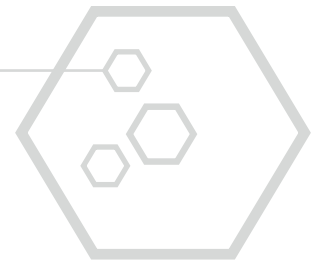


Qualification Versus Validation and Good Cold Chain Management Practices

By Rafik H. Bishara, PhD



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Historically, the terms 'qualification' and 'validation' have been used interchangeably within the cold chain industry. This has led to a significant amount of confusion in the pharmaceutical industry, which could be avoided by standardising the definitions of both 'qualification' and 'validation'.

Background	
Source	Requirements
Code of Federal Regulations (CFR) (1)	<p>The current Good Manufacturing Practice (cGMP) for finished pharmaceuticals clearly defines:</p> <ul style="list-style-type: none"> ◆ Personnel qualifications (education, training, experience) (211.25) ◆ Consultants qualification (211.34) <p>The cGMP requires validation of:</p> <ul style="list-style-type: none"> ◆ Automatic, mechanical and electronic equipment (211.68) ◆ Testing and approval or rejection for components, drug product containers and closures (211.84.2-3) ◆ Control of microbiological contamination (211.113.b) ◆ Testing and release for distribution (211.165.e)
European Union (EU) (2)	<ul style="list-style-type: none"> ◆ Installation qualification (IQ) – the documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturers' recommendations. ◆ Operational qualification (OQ) – the documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges. ◆ Performance qualification (PQ) – the documented verification that facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification. ◆ Process validation – the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting predetermined specifications and quality attributes.
Health Canada (3)	Written procedures for the shipping of drug products should be established and validated. Such procedures should take into account the nature of the drug products and describe any special handling precautions.
Medicines and Healthcare Products Regulatory Agency (MHRA) (4)	Cold storage facilities are qualified/re-qualified.
World Health Organization (WHO) (5)	Validation – the documented act of proving that any procedure, process, equipment, product, activity or system actually leads to the expected results.
USP<1079> 'Good Storage and Shipping Practices' (6)	<p>While completing qualification studies of controlled temperature shipping packages and systems it is necessary to utilise temperature profiles that are expected to be typical for the type of package based on a number of factors including:</p> <ul style="list-style-type: none"> ◆ Temperature conditions at origin and destination ◆ Seasonal temperature (winter versus summer) ◆ Transport routes and modes ◆ Total duration of transit ◆ Duration and location of handling and stop-over points ◆ Overall product handling
FDA 483 Citations	<p>March 2003 FDA 483 citation: "the shipment by truck of finished vials from one site to another is not yet validated".</p> <p>October 2004 FDA 483 citation: "shipping validation was deficient". (7)</p>

The Parenteral Drug Association (PDA) 'Cold chain guidance for medicinal products – maintaining the quality of temperature-sensitive medicinal products through the transportation environment' (8), allows firms to develop their own processes and also to maintain alignment with CDER's General Principles of Process Validation (9):

- ◆ Component qualification (CQ) – establishing confidence that ancillary components are capable of operating within established limits and tolerances
- ◆ Operation qualification (OQ) – establishing confidence that the process is effective and reproducible
- ◆ Performance qualification (PQ) – establishing confidence through appropriate testing that the product produced by a specific process meets all release requirements for functionality

The three qualification components are the foundation of qualification and validation. As these two terms are frequently misused, it is important to first understand how both qualification and validation have been defined by the PDA Pharmaceutical Cold Chain Discussion Group:

Qualification: a documented testing that demonstrates with a high degree of assurance that a specific process will meet its pre-determined acceptance criteria.

Validation: a documented testing, performed under highly controlled conditions, which demonstrates a process consistently produces a result meeting pre-determined acceptance criteria.

Table 1: Comparison of Good Storage Practices (GSP) Versus Good Transportation Practices (GTP)

Activity	GSP	GTP
Handling of product	Static	Dynamic
Manufacturer controls	On-site	Off-site
Environmental impact	Easier to control, less variable	Can be extreme, more variable
Documentation	Complete is standard	May not be as complete or technically difficult
Regulatory requirements	Have been standard for cGMP	Recent expectations by regulatory agencies has increased

While qualification is used to provide a high degree of assurance that a process is replicable under anticipated variable ranges, validation is used to describe how a system will perform under highly controlled conditions.

Based on the definitions above, it is easy to see how these definitions are interchanged. However, the key difference is determined by whether or not the process under review operates under ‘highly controlled’ conditions.

The manufacturing environment operates under cGMP-based processes and – by definition – is ‘highly controlled’. Therefore, manufacturing processes can be ‘validated’. However, the distribution environment is widely variable and “depends upon a range of factors including points of origin and destination, article and container sensitivities to cold, accidental freezing or heat, transit mode (such as air, truck, sea, or combination), time, weather and season, and carrier type (for example, small package carrier or integrator, freight forwarder, US Postal Service)” (6) and therefore operations in the distribution environment cannot be validated – they can only be ‘qualified’. A comparison between Good Storage Practices (GSP) and Good Distribution Practices (GDP), in Table 1, shows the difference between the two environments. Figure 1 (see page 106) shows the proper use of the ‘qualification’ and ‘validation’ terms as they apply to the manufacturing, storage and distribution processes.

GOOD COLD CHAIN MANAGEMENT PRACTICES (GCCMP)

Regardless of how an individual or an organisation may define ‘qualification’ or ‘validation’, ensuring the quality of the product and patient safety is the basis for good cold chain management practices (GCCMP).

As outlined in USP <1079> good storage and shipping practices (6), while completing qualification studies of controlled temperature shipping packages and systems, it is necessary to utilise temperature profiles

that are expected to be typical for the type of package based on a number of factors, including:

- ◆ Temperature conditions at origin and destination
- ◆ Seasonal temperature (winter versus summer)
- ◆ Load configurations
- ◆ Transport routes and modes (overnight air, ground, international and so on)
- ◆ Total duration of transit
- ◆ Duration and location of handling and stop-over points
- ◆ Product handling

By studying these variables in multiple combinations, an organisation is able to gain a level of confidence regarding how their packaging, processes and actions of their contracted service providers will work together with the common goal of safeguarding a product during storage and distribution.

While quality principles are used to reliably qualify the cold chain distribution process, it is to be acknowledged that even a qualified process is subject to change over time. Therefore, periodic and appropriate monitoring is recommended. The frequency and type of monitoring will be based on the specific conditions of a given distribution process.

USP <1079> good storage and shipping practices for qualification of cold equipment or stores states: “Qualification procedures on a regular basis should be independently conducted on equipment in cold stores to guarantee suitability and proper functioning. The procedure should demonstrate the temperature profile for for both air and product temperatures when empty as well as when loaded.” Furthermore, as listed in USP <1079>, “the Prescription Drug Marketing Act of 1987 and 21 CFR Part 203, Prescription Drug Marketing, and Part 205, Guidelines for State Licensing of Wholesale Prescription Drug Distributors, provide the necessary regulations and guidance for several legs of the distribution chain for the prescription drug. The

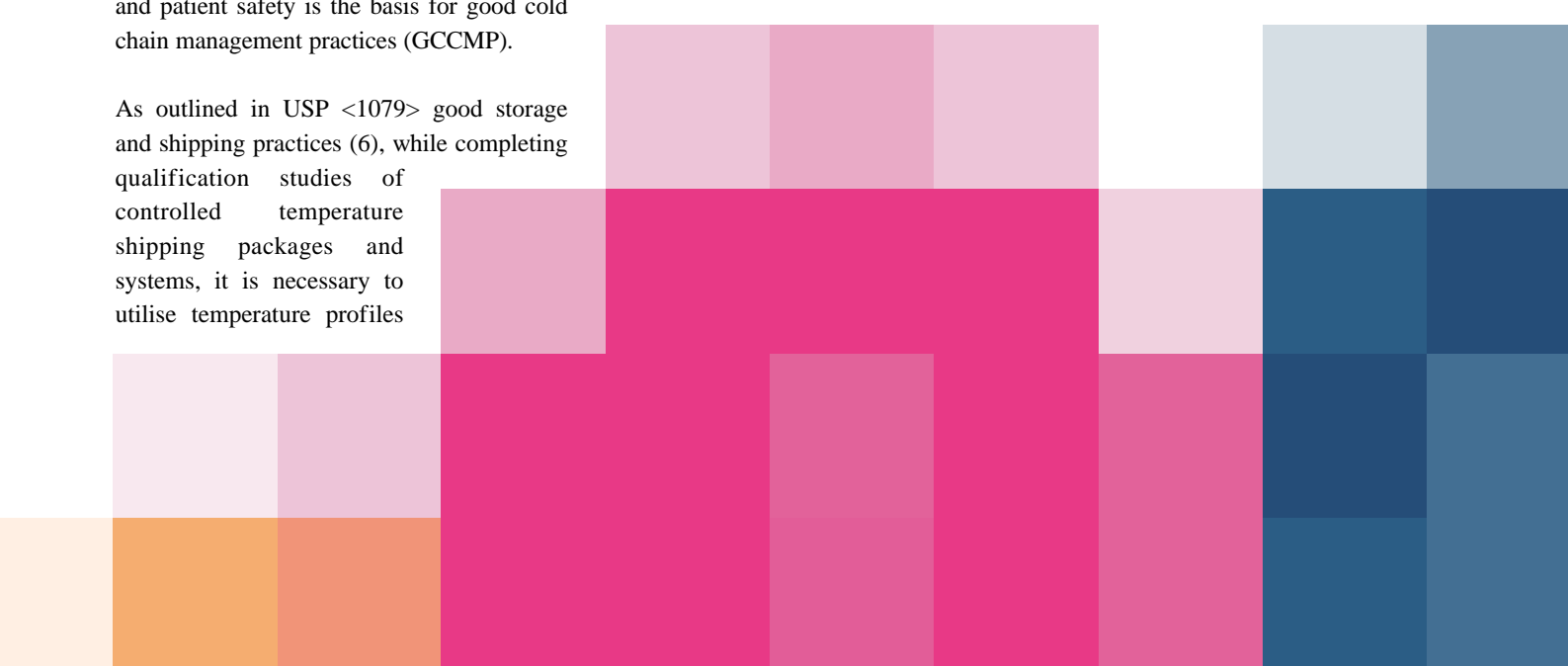
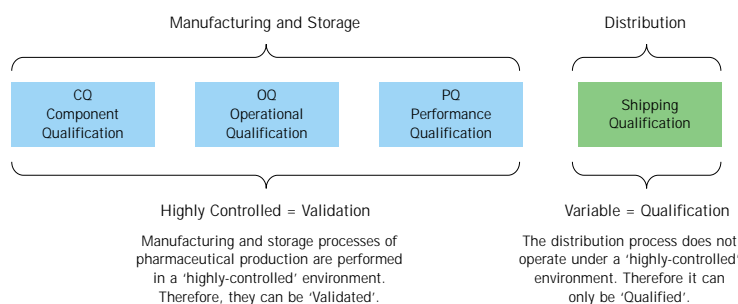


Figure 1: Qualification Versus Validation



CONCLUSION

The standardised use of qualification, validation and good cold chain management practices (GCCMP) will be beneficial for all involved parties in handling, storing and distributing environmentally sensitive pharmaceuticals. An ongoing monitoring programme will provide data to make the quality decision for each shipment. ♦

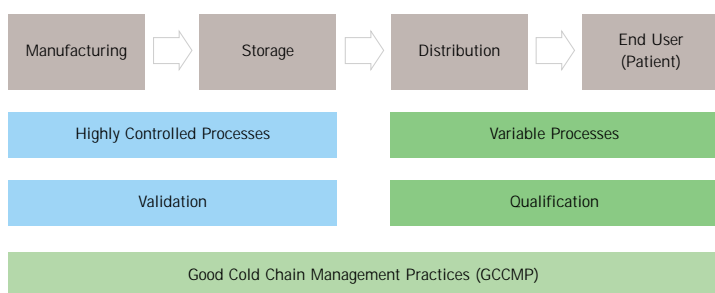
Note

The concept of this paper was presented at the 3rd Annual Cold Chain Storage and Distribution Conference, 22-23rd September 2005, London, UK.

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Figure 2: Good Cold Chain Management Practices (GCCMP)



manufacturers and distributors should work together to establish proper distribution and product-handling requirements for the purpose of ensuring appropriate product maintenance in transit.”

It is then recommended, for the sake of eliminating confusion, to adopt a consistent use of the terms ‘qualification’ and ‘validation’. In addition, the promotion and use of GCCMP is recommended in determining and performing the proper handling, storage and distribution of environmentally labile pharmaceutical products. Within GCCMP, ‘qualification’ should be used for processes that are replicable under variable conditions while ‘validation’ should be used for those processes that are performed under highly controlled conditions (see Figure 2). A GCCMP system will then meet all of the above requirements.

ONGOING MONITORING

Based on the above, we recommend establishing an ongoing temperature and humidity monitoring programme for the shipment of environmentally sensitive medicines. A shipping container that has been ‘validated’ under highly controlled conditions is subject to unknown variability in the distribution channel and may therefore not be sufficient to guarantee a product’s integrity and efficacy at the time it reaches the final customer (the patient). Only an ongoing monitoring programme is capable of generating the data required to support appropriate quality decisions related to the storage, shipment and final distribution of temperature-sensitive pharmaceuticals.

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