Risky Move

Patient access to medicines is a rapidly evolving challenge for the pharmaceutical industry. As the complexity of the marketed therapies increase, and the shift from small molecule drugs to biologics and regenerative therapies accelerates, companies are re-evaluating their supply chain strategies

Mark Sawicki at Cryoport

Most pharmaceutical organisations employ specific strategies based on ICH guidelines Q8-Q10, which provide high-level guidance outlining a risk-based approach to evaluate processes and implement strategies to control and improve pharmaceutical quality throughout the product lifecycle. The majority of firms rely on these guidelines to help mitigate risk in their supply chains, including manufacturing, suppliers, sales and product design, as well as logistics activities such as bulk packaging, transportation and distribution strategies.

However, these conventions must be challenged and restructured to incorporate the latest technologies and processes when distributing the new, more temperature-sensitive regenerative therapies. The reason for this is both vital and straightforward: a single temperature deviation during transit can destroy a $750,000 product and potentially lead to the death of a patient. Even if a temperature deviation does not have such a dramatic result, it may still lead to seriously compromised data and clinical trial outcomes.

Supply Chain Quality by Design

Companies transporting these sensitive materials must consider employing a proactive Supply Chain Quality by Design (SC-QbD) process for the distribution of clinical and commercial materials. QbD is driving new guidelines in the industry – including the soon to be published ICH Q12 – which deals with pharmaceutical product lifecycle management and is intended, in part, to strengthen proactive planning of supply chain adjustments (1).

To better understand the logistics parameters and factors that directly impact commodity integrity, it can be useful to complete a comprehensive scientific study on the impact of packaging, transportation and temperature ranges on the viability of cells, biomarkers and critical reagents for pharmacokinetic/pharmacodynamics, immunogenicity and clinical studies (2). The outcome of the study can substantiate logistical concerns, such as the tangible impact of packaging, logistics and handling on the quality of the materials being transported at dry ice and cryogenic temperatures.

In one such study, it was demonstrated that significantly greater standard deviations related to temperature resulting from shipments using dry ice were responsible for the variability in the % recovery of biomarkers shipped and % viability on cell lines shipped. It was also observed that multiple factors – including packaging, loading, orientation, temperature, shock, transit duration and refrigerant – work in a complex and cumulative manner to affect the commodity being shipped. Moreover, traditional qualification and validation procedures like International Safe Transit Association (ISTA) 7E testing, while important, cannot dynamically account for the impact of these factors during transit.

ISTA Testing

ISTA has been working to address the increasing variability associated with industry testing as well as the dynamic factors related to logistics sample management. This includes the recently released ISTA Standard 20 Revision 2, a process

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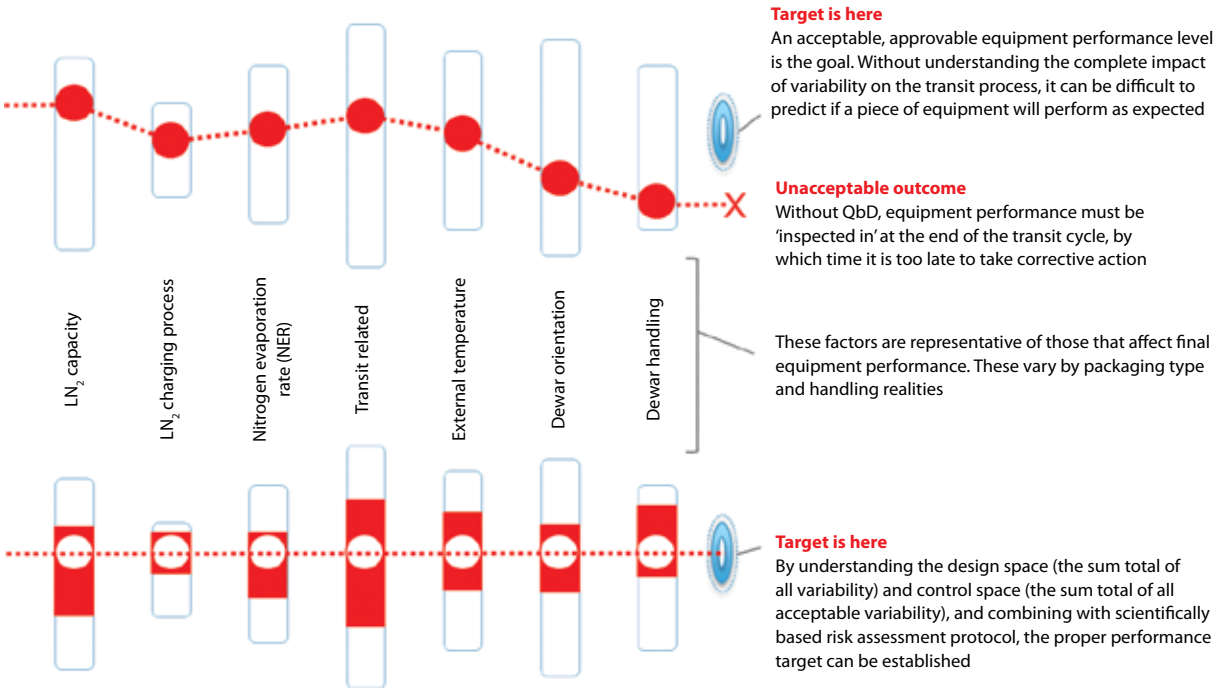

Figure 1: QbD methodology for cryogenic shipments

standard developed by pharma industry experts. ISTA Standard 20 is "a design and qualification process that provides the structure and path to design, test, verify and independently certify a specific Insulated Shipping Container (ISC) for use. It sets the minimum requirements for qualifying insulated shippers and has been proven to develop shippers which meet regulatory expectations. Included with Standard 20 is the Standard 7E set of global thermal profiles" (3).

ISTA Standard 20 is an important development in the industry as it standardises the testing regimens and measurement tools related to the insulated shipping container. It can be augmented in a significant way by improving the data collection, measurements and analytics of the processes related to the handling as well as transportation of the insulated shipping container.

Innovative Process and Technology

To be most effective in mitigating risk during cold chain transport, pharma needs to embrace evolving scientifically driven quality processes and start to adopt cutting-edge

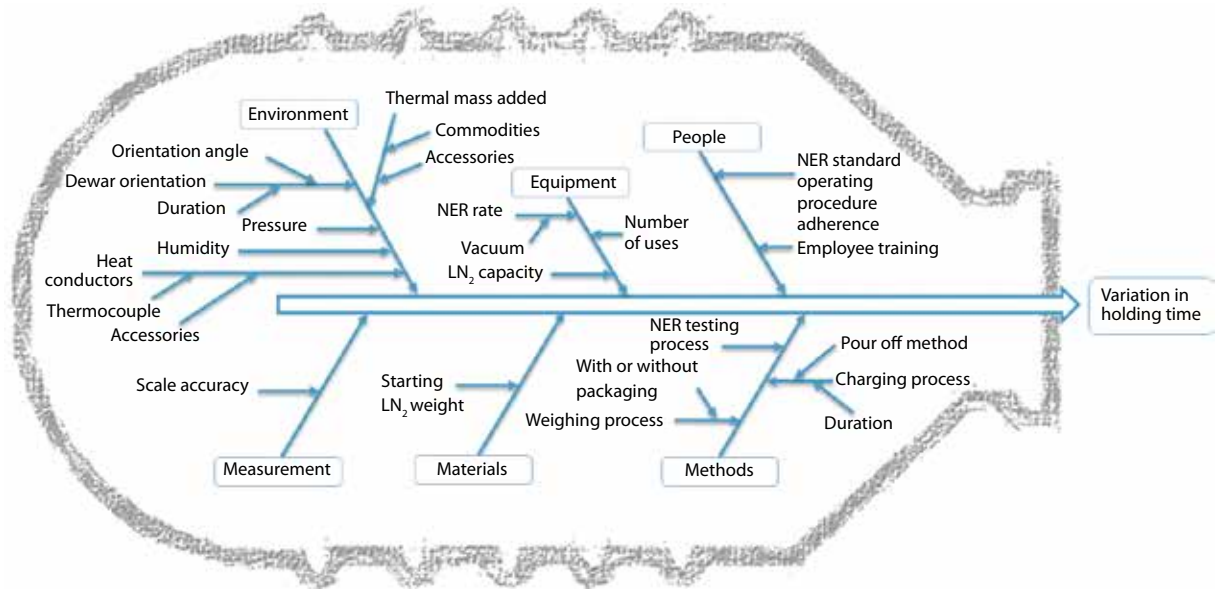

Figure 2: Process variables using a standard shipping dewar

technologies, in order to better understand and control the variables that impact material integrity. By leveraging innovative shipping technologies – like continuous monitoring, for example – the industry could achieve better visibility of the dynamic handling and conditions of the biologic material (and its packaging) throughout its journey. Most importantly, having this information enables intervention to remediate issues that arise during shipment. This real time data provides a significant analytical tool to develop and implement actionable design of experiment (DOE) and QbD methodology into the distribution process.

The QbD process is a systematic approach to development that begins with predefined objectives, and emphasises product and method understanding as well as process control based on sound science and quality risk management. DOE can be used to determine the relationship between factors affecting the transportation process – such as packaging, loading, orientation, temperature, shock, transit duration and refrigerant – and the output of that process, often referred to as the chain of condition. In other words, DOE is used to find cause-and-effect relationships that can be leveraged to manage process inputs to optimise the output using a QbD methodology. An example of this method on cryogenic shipments is illustrated in Figure 1.

In this example, elements such as the liquid nitrogen (LN_2) capacity, nitrogen evaporation rate and orientation of the dewar being shipped vary with each shipment, and can change materially from one use to the next. Having the ability to dynamically measure and account for these factors on every shipment and for every dewar provides the ability to utilise QbD processes to better mitigate risks. Static qualification and validation processes cannot account for these changes dynamically and introduces unmeasurable variability that can impact the hold time of a dewar by as much as 50%.

Moreover, the number of variables in the process of using a standard shipping dewar can be significant (see Figure 2). This variability is not limited to dewars alone – standard packaging employed daily for temperature ranges from controlled room to dry ice temperatures are subject to similar handling and transportation risks.

In the same study mentioned above, the orientation of the packages during transport, and the resulting impact on the temperature as well as hold time, were evaluated. The packages were routinely misoriented and subjected to significant shock events in 65 of 66 instances during the study. In fact, regardless of package type, they were misoriented approximately 15% of the time (see Figure 3, page 64). Misorientation of the dry ice packaging reduced hold time resulted in significant pH changes in the samples and increased temperature volatility. Table 1 (see page 64) shows the average temperature and standard deviations

	Styrofoam	Vacuum	Dewar
STDEV*	14.1	7.6	0.7
STDEV (+)	-57.9	-69.2	-192.9
Average	-72.0	-76.9	-193.6
STDEV (-)	-86.1	-84.5	-194.3

**Standard deviation (STDEV)*

Table 1: The temperature volatility of the three different shipper types (°C)

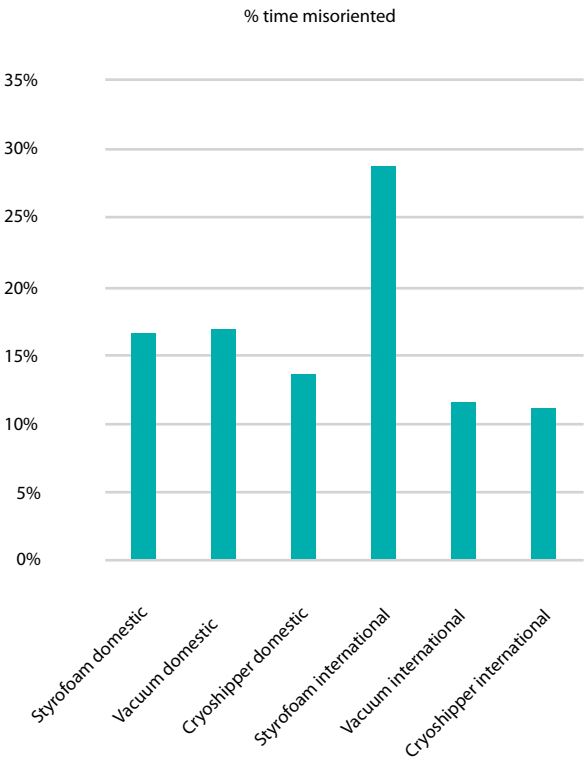

Figure 3: Graph illustrating the % of time each package type was misoriented more than 20°C from an upright position

associated with the misorientation of three different package types. While temperature volatility was not observed in the cryo shipments, the hold times were notably impacted by improper orientation due to increased nitrogen evaporation rates.

Real Time Integrity Measurements

What is clear is that, to establish and implement effective tools, processes and systems that support a QbD methodology, for logistics support, transportation and packaging considerations must be approached with scientific rigour. As a first step, companies need to evaluate packaging and transportation against current ISTA guidelines. Additionally, they must use scientific processes to evaluate the various factors related to transportation independently and as an aggregate to determine their impact on product quality and integrity.

Utilising resources early to clearly develop and establish effective DOE processes for use in a QbD methodology and assessing the necessary scientific data that will enable intelligent decisions, can be expected to improve the quality of the material being transported. Furthermore, once the variables determined to be critical to the standard of the material shipped are identified, tools that measure these impacts in a continuous manner must be instituted such that a dynamic picture related to commodity integrity can be measured in real time. For example, if a cryo shipper in transit is misoriented, the hold time of the dewar can be adjusted based on the orientation angle and change in nitrogen evaporation rate. This type of system will provide more control over the process and the resultant impact on the commodity.

The consequences of not adopting this methodology include introducing additional risk in the process and the resultant data generated from the materials being transported. This may lead to companies making critical decisions on clinical endpoints using compromised data generated through biologic samples of unknown quality. Such decisions, if based on faulty data, may impact trial outcomes or increase overall spend and duration due to sample loss.

References

1. **Visit: www.ich.org/products/guidelines/quality/article/quality-guidelines.html**
2. **Visit: www.cryoport.com/resources/the-science-behind-logistics-how-cold-chain-planning-impacts-the-clinical-development-and-commercialization-of-regenerative-therapies**
3. **Visit: www.ista.org/pages/procedures/ista-standards.php**

About the author

With more than 15 years' experience in the pharma and biotech industries, **Mark Sawicki**, PhD, serves as Chief Commercial Officer at Cryoport, a company that provides end-to-end cryogenic logistics solutions to the life sciences industry. He holds a Bachelor's degree in Biochemistry from the State University of New York at Buffalo, US, and a PhD in Biochemistry from the University's School of Medicine and Biomedical Sciences.

Email: msawicki@cryoport.com