



# SETTING NEW STANDARDS



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WITH THE EVER EVOLVING DEVELOPMENTS IN THE BIOPHARMACEUTICAL INDUSTRY THERE HAS NEVER BEEN A GREATER NEED FOR ASSURED RELIABILITY WHEN IT COMES TO THE TRANSPORTATION OF PHARMACEUTICAL PAYLOADS AND THE GUARANTEED ROBUSTNESS OF TEMPERATURE-CONTROLLED PACKAGING IS PROVING EVER MORE VITAL.

The continuing growth of, and increasing move to, the implementation of large molecule medicines naturally calls for greater reassurance of temperature-controlled packaging reliability and the life sciences industry, as well as the packaging industry, would benefit from an all encompassing, standardized measure of performance when it comes to temperature-controlled systems adopted to transport often high-value assets.

There needs to be a more universal approach for a standardized measure of performance. Currently many vendors demonstrate the performance of temperature-controlled packaging by showing an example of performance, most often carried out with an ambient profile that shows how the temperature-controlled packaging will respond to a particular simulated shipment route.

However this method has its drawbacks. Currently the go to industry standard for performance regularity is mainly via the International Safe Transit Association (ISTA) which represents a collaboration of manufacturers, packaging suppliers, testing laboratories and carriers working together to try and ensure responsible packaging.

Previously organizations like ISTA have tried to create a standard profile that they say captures in essence the worst case scenario of what could happen in any given transport situation, however what that ends up doing is further widening the possibilities of creating packaging that might not always be fit for purpose. The problem is companies might then end up with packaging that is overdesigned for the actual challenge of what the customer actually wants to use it for.

ISTA's initial focus was on the mechanical testing sequences, used to prove the robustness of over-packaging for every day products such as ovens and washing machines. More recently ISTA developed thermal test procedures for insulated packaging and one of the profiles widely adopted in standard qualification, ISTA 7D, and more recently ISTA 7E is by some seen as an industry standard.

With the emergence of the new generation of biopharmaceutical medicinal products, coupled with the emergence of new, remote and logistically challenging markets, the issue of being able to deploy reliable, high-performing shipping systems is paramount. This rapid rise in biopharmaceuticals, generating global revenues of \$163 billion, equates to somewhere in the region of 20 per cent of the pharmaceutical market, making it by far the fastest growing part of the industry.

## Industry-wide Standards

Having to transport pharmaceutical products via challenging shipping routes, further facing the likelihood of being exposed to greater temperature stresses or unplanned hold periods (such as customs clearance), makes the introduction of a new industry-wide standard performance measurement something that should be at the forefront for decision makers.

There needs to be a collaborative call for a new industry standardized measurement system that is easy to implement and can be adopted worldwide within the sector. There is an even greater urgency to address the situation especially with the new generation growth of biopharmaceutical products that are highly temperature sensitive and must be stored and transported within the specified temperature range.

Why not implement a thermal stress score, a standardized procedure, calculated by stress testing with universal acceptance?

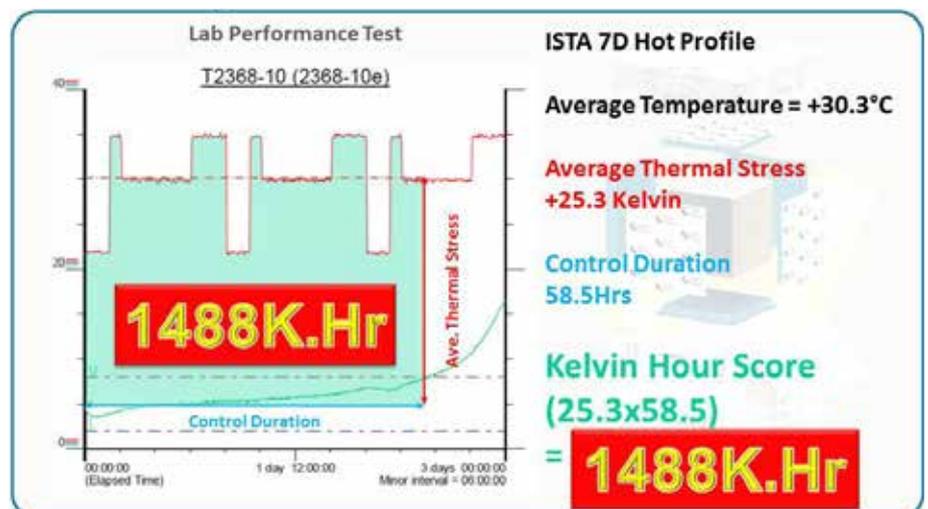
## Kelvin Hours

For greater reliability the industry is calling out for a standardized method such as Kelvin Hours (KH), which could be universally adopted and recognised as a new industry standard for the global temperature-controlled packaging industry. It brings to the fore the shipping system's performance capabilities.

The benefits of adopting Kelvin Hours as a standard performance measure is that it doesn't tie itself to a particular ambient test profile. Rather it is centred on what the specific selected shipping system is capable of doing and therefore you can say against ambient profile X, Y or Z that particular shipping system will perform for a specific number of hours for those different challenges, so it makes it less subjective and more of a measured approach.

With this proposed KH principle you could collate your Kelvin Hours via a simple equation - average thermal stress (K) x control duration (hrs) = K.Hrs. Adopting this calculated stress testing, using vendor qualification data, enables easy fit for purpose evaluations.

FIG 1: Kelvin Hours: examples of how to calculate (average thermal stress x control duration = KH)



Kelvin Hours could easily be adopted as a tool to select the most appropriate level of performance of packaging and this can be used across the board with a broad range of performance points for the newer style Phase Change Material (PCM) systems which is where the Kelvin Hours measure works particularly well.

A company using temperature-controlled packaging can assess shipping lane data using Kelvin Hours and select a packaging system, which satisfies the minimum performance requirement. Essentially what you have done is you have matched the shipping system to the challenges it is going to face as opposed to having one shipper option and then finding out that you've used only half of its potential performance in your particular shipping lane.

### Performance Reliability

The need for a new, standardized measure of performance was not so pronounced previously when it came to the shipping of the small molecule pharmaceutical products, which were potentially less temperature sensitive.

The new generation of large molecule biopharmaceutical products, which are being developed for relatively rare conditions, such as the various cancer treatments, rely on high-performance packaging systems to avoid their complex, fragile structures being destroyed.

These more sophisticated pharmaceutical medicines being developed to help people overcome or live with, certain diseases, are a vital lifeline for patients who are reliant on them which is why it is paramount these drugs arrive intact and perform properly.

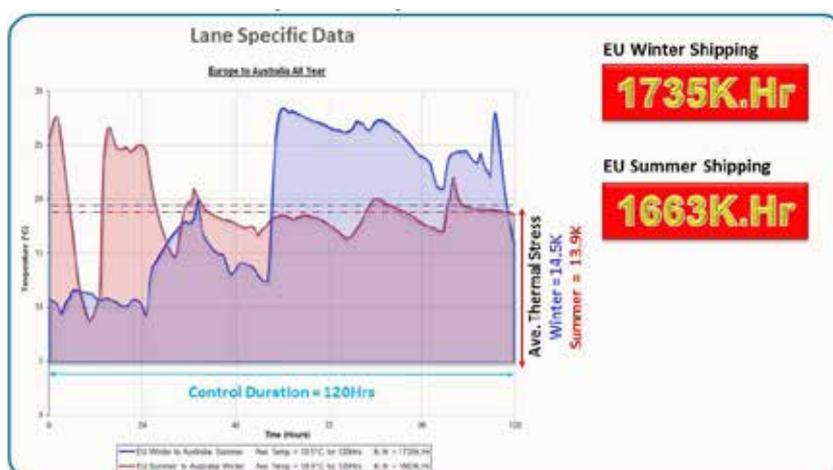
For pharmaceutical companies developing products to treat such conditions reliability in shipper performance is equally critical within the clinical trials industry where the materials that are being shipped are designed to be tested on "in human" at Phase 1 clinical trials.

It is at that fragile stage where pharmaceutical companies haven't got any stability data for the medicines being trialled, so they can't afford to let it go outside of a temperature window, and what is required is a more robust shipping system. These systems are crucial not just for the safe transportation of the medicines being trialled but also when it comes to shipping the comparator drugs.

### Clinical Trials

When it comes to clinical trials, and the development of a new pharmaceutical product, it has to be trialled against drugs similar in the market most usually being sold and manufactured by a competitor so pharmaceutical companies have to buy these products at market value, which is often extremely expensive. Coupled with the fact these companies don't have access to any stability data they have to ship the payload within a strict temperature range to know it is going to be as effective as it should be and therefore prove its worth as that comparator against the product they are developing.

FIG 2: Appraise lane characterisation data example: Europe to Australia (all year)



The cost implications related to comparator drugs testing can be extremely high and can constitute up to half of the clinical trials total budget allocation.

Therefore if that comparator drug goes to waste because the packaging selected for the transportation fails to meet the high standards necessary and is substandard as it didn't have a well defined performance measure, the costs can be unbelievably high with, for example, a 10ml vial costing tens of thousands of dollars for a single dose.

### Kelvin Hours Scoring System

Acting as one of the drivers for the introduction of an industry wide standardized measure of performance such as the Kelvin Hours, is the development of these large molecule products. This is an example of where a standardized and globally adopted performance measure such as Kelvin Hours will become increasingly relevant in the future where people can't take the chance on something not working. They need that reassurance the packaging has been specified well and it will deliver it for them.

The growth of gene therapies and manipulating proteins in research into certain conditions like cystic fibrosis, are also proving to be strong drivers in a suggested shake up of the current systems.

The introduction of a more standardized measurement system would have Industry wide relevance. Especially so in the clinical trials market where large, global pharmaceutical companies are focusing their research and development increasingly in the high value niche application products.

If this new Kelvin Hours approach was adopted across the industry there would be different levels/points of performance so you end up with different Kelvin Hours Scores which in turn would make it easier to match that with the appropriate shipping system required.

Technically speaking the industry could use a Kelvin Hours scoring system, which appraises performance, at the actual stage of preparing the packaging.

This could revolutionize the packaging industry and rather than selecting a shipper for a particular duration it would be a case of selecting the appropriate shipper with the relevant Kelvin Hours Score (KHS) attached to it. For further ease of use a customer could describe the challenges of their specific shipping lane and receive a score that would help them choose the best packaging product for their needs.

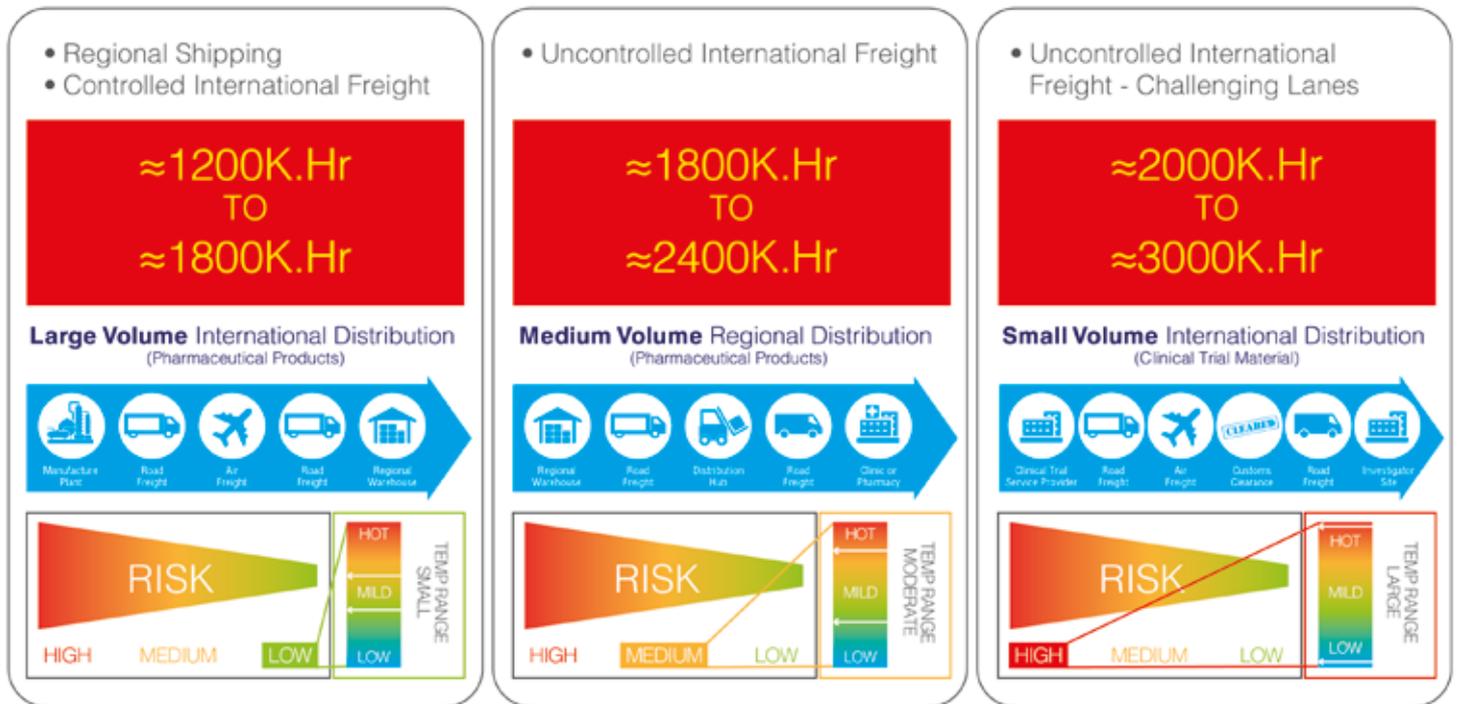
This would also have great cost effective repercussions as it would help prevent picking a product that has been over engineered for the challenge or job it is actually required for.

The wider this suggested system was adopted it would mean in the future it would be much easier to compare one set of products against another. It means you can really compare 'apples with apples' whereas at the moment because there are all these very different ambient profiles being used in the industry, performance, or the appreciation or perception of performance, can be skewed. The KHP works extremely well with newer PCM systems and where it probably needs a little more development is when trying to use that same performance measure for the older technology, water based systems.

In a bid to make the KHP measure a bit more robust it would require trying to build in an additional aspect that takes into account the inefficiencies of the old technology systems to make it truly all encompassing.

Most of the new product development we are seeing in the temperature-controlled packaging industry incorporates the newer, more advanced materials but there is still a significant proportion of the market using the older, water based systems purely due to the cost restraints.

FIG 3: Match the 'challenge' to the most appropriate shipping system



You've got the packaging suppliers who might have their own set of ambient profiles they qualify their packaging against. What we also see is that some customers will request packaging suppliers to qualify against their own ambient profiles which they see as being indicative of what they would expect during distribution of their product from one location to another. The issue is every single customer will have a different view on what that looks like.

So you haven't just got different vendor profiles, you've got different customer profiles and ideally because the whole qualification process is extremely time-consuming, it would be beneficial to make the process simple and quick.

Therefore a new, industry-wide performance measurement would benefit not just packaging suppliers but also those who have to specify the packaging. It could be a performance measure which, as long as they have got visibility of the temperature challenges they expect to see in a shipping lane, they can use it to create this stress score, this KHS, and then simply go into the market place requiring a box capable of a certain KHS. In theory whichever suppliers have packaging tested to the standardized KHS should have the shipper most appropriate for the job.

### Testing Times

Over the last five years there has been a notable rise in the temperature monitoring of pharmaceutical products. Depending on which region you are shipping into. For example emerging markets such as the Middle East, when that package reaches customs control, if they see it is a temperature sensitive package with a data logger inside it, they may have to open the package to inspect the data logger and make sure it is still within temperature. If it has not been maintained at the correct temperature up to that point the package could be sent back.

The industry needs change, especially the pharmaceutical industry, for these ever more sophisticated medicines to be effective. If they get too hot or cold and if they are protein based the proteins can denature so that medicine, which is potentially going to help to cure a patient or help relieve their symptoms, could, if exposed to too high or cold temperatures for too long, lose efficacy – jeopardizing what could be life-saving treatments for patients.



### About the author

Richard Wood, Design Manager at Peli BioThermal, has worked in various design and manufacture engineering functions during his career.

He has worked for Peli BioThermal since 2005 and has been involved in hundreds of cold chain packaging projects.

Richard has helped to ensure manufacturing practices are standardized across the Peli BioThermal global network.

Richard's current role within Peli BioThermal is focused on standardized development, qualification and manufacturing practices to help support their global customer base and he also leads their New Product Development program.

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