COLD CHAIN CONSULTANTS

ANNUAL REPORT 2014

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TO OUR READERS

Each year Cold Chain Consultants publishes our annual report providing the industry with a global perspective on the previous year's observations from our global activities. Our report summarises the past years focus points of the industry, regulators and provides insight and guidance on what could be expected in the coming year. We also highlight many of the challenges facing the industry and approaches to solutions.

In 2014 we have seen more activity and focus on the temperature supply chain for pharmaceuticals and medical products than ever before. There is no doubt the regulators across the world are taking a more in-depth review into supply chain practices.

The number of multimillion dollar supply contracts won and lost to government agencies, hospitals, 3PL companies, transport companies, distributors and manufacturing sites over the past year directly attributed to the temperature supply chain, demonstrates the significance of the change in the industry.

Cold Chain Consultants

REGULATORY REVIEW

After the release of the EU GDP guidelines in Nov 2013 we only observed a enforcement during inspections and audits. Much of the questioning centred on gaining an understanding of temperature supply chain practices and qualification methods uses by industry. We noted in several global markets there was a significant increase in Controlled Room Temperature (CRT) supply chain qualification after regulatory audits. There is still significant negativity around the cost of increasing compliance within the temperature supply chain and with the increasing costs estimated between 30% and 200 % it's not surprising.

The positive side from the introduction of the EU GDP guidelines is the global standardisation and the efficiencies which can be gained from many countries adopting the same reference document. We have observed over the past year that emerging countries and markets without the regulatory experience of the EU, UK and USA are adopting the EU GDP guidelines as guidance documents for their regulatory inspections.

Source: 2013 UPS Pain in the Chain Survey Results

In 2014 the MHRA announced they were employing new inspectors to focus on GDP compliances in the temperature supply chain. This announcement is a strong indication there will be a concentrated focus on temperature qualification in the supply chain for Cold Chain and CRT products from the UK Regulator. It has long been a view by the MHRA that storage temperatures printed on the packaging labels must be maintained during storage and distribution. In previous statements their view was

Over the past 3 year we have seen many CRT warehouses quarantined by regulators across the world for temperatures above 25°C during the hot days of summer with some only exceeding storage temperatures by a few degrees. These findings were then extended to investigations of the whole of the CRT supply chain. Life cycles of the product is another focus for regulators and these statements are appearing in many press release reports and guideline statements from the FDA and MHRA respectively.

REGULATORY REVIEW

Two quotes from inspectors over the past year are particularly worth noting and the message they convey:

- When a company complained about the cost of implementing temperature control for their CRT products the reply was "I have no concern for the costs, my priority is patient safety" they went on to say "the safe storage conditions are printed on the packaging for the market approval and it is expected you store and transport within the conditions.
- Another company relied on and presented as a part of the documents qualifying the supply chain some Technical Reports and industry white papers to justify their methods. The view of the inspector was- "Industry reports are useful tools and provide some knowledge and insight from the industry, however they are not the Law and we require you to demonstrate the storage temperature in the supply chain is maintained".

Announcements

The below extracts from the latest FDA report for 2014 to 2018, are worth noting as they relate to many of the topics we highlight in this report and support our findings from the field.:

"Globalization demands that FDA think act, and engage globally. FDA's success in protecting the American public depends increasingly on our ability to reach beyond US borders. FDA must engage with our government regulatory counterparts in other nations, as well with industry and regional and international organizations, to encourage the implementation of science based standards that ensure the safety and quality of products before they reach the United States. Safety and quality are integral to FDA's mission of promoting and protecting public health. Safety and quality include:

1) *the practices used to make products,*
2) *the integrity of the supply chain that delivers these products to their users ,*
3) *methods for protecting the public, including laboratory sample analyses for select product categories and product.*

Food safety and medical product quality primarily depend on the industry, requiring top –level management commitment: a clear and in depth knowledge of the product and the system: supply chain management throughout the entire life of a product: proactive and continuous management of risk: and continuous and consistent monitoring of quality management systems and processes."

COST & OPTIMISATION

There is no doubt the game has changed and the focus by the regulators in all countries on the temperature supply chain will add significant cost. The only way to minimise the impact of the costs is to fully review and optimise the supply chain. This is only possible through full optimisation of the whole supply chain, trying to optimise segments will not deliver the cost saving or efficiencies required or increase compliance. The challenge for the industry is optimizing any non-temperature supply chain is relatively straight forward, however when temperature control, qualification and monitoring are added there are in excess of 40 variables which must be considered or the optimisation project will fail and add cost instead of reducing it.
We have worked with various new strategies over the past year to optimise temperature supply chains and many new solutions have been created and implemented in different parts of the world. Our main focus has been to challenge the current practices and innovate to improve quality while balancing the costs across the whole global supply chain. We know from experience the only true successful optimisations have come from a holistic approach.

TRAILER, TRUCK AND CONTAINER QUALIFICATION

We saw a significant increase in our consultants writing procedures and conducting thermal mapping of temperature controlled trailers and trucks over the past year. Unfortunately for many of the clients the results were not what they expected. A high percentage of trailers which were being used for pharmaceutical transport were not suitable for purpose, despite being used for many years and reported to have been previously qualified.

During the course of the year we sighted an increase in Reefer sea container and airline container qualifications. These can also present challenges when qualifying these units and if the processes and qualification is not properly conducted it will result in temperature excursions and failures to maintain temperature.

RISK ASSESSMENT

Risk assessment has been a major part of Cold Chain Consultants work over the past 2-3 years. This has also been a high level of focus at regulatory inspections, it is expected to demonstrate the risks are fully understood and the risks identified are minimised.

One of the largest failings in this area has been the Risk assessment document's lack of detail and identification of the real risks. Another common failing is the risk assessments written to justify the practices which are quickly questioned.

In the coming year we anticipate even more focus by the regulators on the risk assessment of the temperature sensitive supply chain and encourage the industry to be prepared. Simply making statements in a risk assessment without supporting evidence will not pass a future inspection.

GDP TRAINING

In the past year we have noticed less attendance numbers at our public GDP training workshops with a trend towards more customised in house GDP training.

In an effort meet our customers' needs in today's busy environment, CCC shall be launching remote learning modules in a number of electronic formats which will allow the students to access the training modules and sessions over a wide range of variable time zones to suit their specific needs. The request from industry was for a more flexible and interactive learning approach and to cater for participant's busy work and travel schedules.
We had feedback from industry about the requirement for more in-depth knowledge and advanced training to understand the technologies used in the industry and for training on the correct ways to qualify the temperature supply chain.

We will also be introducing an advanced training for GDP qualification in the coming year. Please refer to the CCC website www.coldchainconsultants.com for more information and training sessions which shall commence Q1 2015.

SUPPLY CHAIN QUALIFICATION

During the course of the year we have observed activity in the qualification of temperature supply chain and it is important to focus on the most pressing and identified risks. As the world is focussed on the EU GDP guidelines as the industry bench mark for pharmaceutical temperature supply chain, it should be noted the guideline focuses on temperature, process, documentation, responsibility and qualification.
Temperature is a largest focus due to it being the easiest to monitor, measure and everyone understands the impact of temperature on products. The safe storage temperature is printed on the packaging and therefore easily identified by everyone in the supply chain and the easiest to control.

Additionally, there was a high level of focus on humidity, vibration and shock in qualifications, however there is minimal guidance written in the EU guidelines or other regulations and guidelines on the compliance requirements. Shock, vibration and humidity are very difficult to control in the supply chain, however it would be wise to consider the impact and justification to consistently measure these specific areas. Shock, vibration and humidity may present risks to some products quality and should be identified and considered in the risk assessment.

We recommend focusing at this time, resources and energy on the temperature qualification of the supply chain, in line with the current regulatory inspection focus.

We strongly support the temperature focus as every day in the field we identify hundreds of temperature excursions potentially harming product quality. The industry has a long way to go to demonstrate to the member countries of PICs the temperature supply chain is properly qualified.

INSPECTIONS OBSERVATIONS

New product registrations

Over the past year we have observed new product registration delays when companies are being asked to provide more information on the temperature supply chain. This is one method regulators are employing to force change and better practices throughout the supply chain. The submissions now require substantial documentation and detailed evidence that the supply chain for the new products will control the storage conditions through the entire supply chain as printed on the packaging.

Border Inspections

There has been a significant increase in regulatory agencies cooperating with the customs and border protection departments to monitor the temperature within the supply chain. We can expect in the coming year this will only increase. Delays at the border are often caused by failures in the documentation. To minimise delays we recommend a full review of internal procedures and implementation of a robust checking system. This will prevent the delays if the qualification of the supply chain is of a high standard and temperature excursions are not detected.
We have clients who advise they do not experience regular delays due to their robust systems and checks before shipping.

Temperature Monitoring

We have observed companies voluntarily implementing and inspector's pressure forcing the temperature monitoring of every shipment, the cost is often considered small however the long-term implications need to be considered. Temperature monitoring will highlight every weakness in the supply chain and usually creates a significant increase in QA work to release shipments with excursions. More importantly the records of the excursions will often be reviewed at the next inspection. A significant percentage of products released from transport quarantine using stability data will be noted in future inspections and indicates to the inspector the temperature supply chain isn't under control.

It is standard practice for Cold Chain Consultants to conduct a GAP audit on the supply chain prior to implementing the temperature monitoring and we highly recommend this as a step first in improving your temperature sensitive supply chain. Identify the GAPs and introduce corrective actions with qualified systems in conjunction with temperature monitoring to avoid this trap.

Documentation

With the risk based approach to regulatory audits now common place, one of the largest failures is documentation. The completeness, quality and detail within many documents are failing to comply with the expectations and requirements. The level of detail is often insufficient and supporting documentation often has GAPs or very little underlying supporting information. The expectation at inspections for the quality of supply chain documentation is much higher than we have seen in previous years, with many processes and qualifications related to the supply chain being challenged. It is not only the pharmaceutical companies GMP sites documentation but the whole of the supply chain being reviewed down to the last mile. The lifecycle of the product being the justification for the review of the whole supply chain.

INSPECTIONS OBSERVATIONS

CRT - Controlled Room Temperature

The focus of the regulators continues to be directed toward this important temperature bracket within the supply chain, during our GAP audits and process reviews we have observed an alarming amount of CRT products transported in uncontrolled conditions with testing stability data between 0°C and 40°C. We also found many liquids and creams that had storage conditions store below 25°C and were transported in uncontrolled conditions which exceeded the stability testing data temperature limits of the products

Over time complacency creeps into all processes and CCC recommends a review across your supply chain before the next inspection.

Temperature Excursions

Over the past few years Cold Chain Consultants have been called to investigate the loss of millions of dollars in quarantined product through temperature supply chain and cold room failures. We have been able to save a large percentage of the quarantined products and return them to the supply chain with the approval and release by the quality departments, and saving companies millions.

What to do in case of a failure or discovered excursions:

- ⇒ Take multiple photos including close ups and panoramic views from every side.
- ⇒ Place the product in Quarantine (Physically and Electronically)
- ⇒ Record as much detail as possible on the events leading up to the discovery and what processes took place prior, ie a sequence of events timeline.
- ⇒ Interview all staff who were involved in any of the processes before discovery and record what they observed.
- ⇒ It is important to record all times and location with every detail.
- ⇒ When equipment failure is responsible and if possible leave the equipment untouched until the root cause is established.

It is important to leave as much intact and untouched as possible but at the same time move the product into the correct and applicable temperature controlled environment to prevent further temporary excursions. Trace back to the beginning of the process, as often the root cause is well before the failure is detected.

If you require urgent assistance email Cold Chain Consultants and we can assess the next steps. The more you change, move or alter the scene the less chance of saving the product.

Note: When CCC have traced back the root cause of supply chain failures 90% of excursions are set up to occur before the product leaves the warehouse.

INSPECTIONS OBSERVATIONS

Cool Rooms Qualification.

During 2014 we conducted a large volume of cool room and warehousing qualifications and requalification's. Many failed to maintain consistent temperatures and often temperature alarm systems were set with very long delays to avoid alarms where the cool rooms were operating out of specification. See examples below Figure A and B. Results in °C (Celsius)

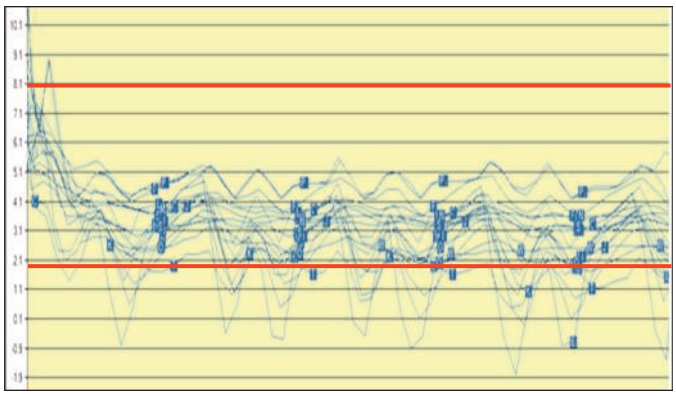

Figure A- shows an example of a thermal mapping results of a cool room which has not been properly qualified.

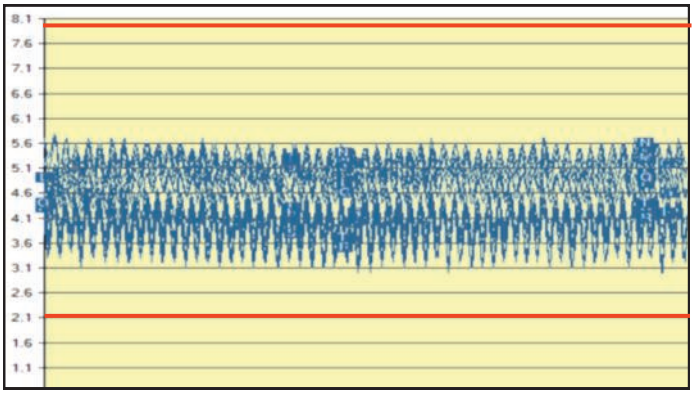

Figure B- show the results after Cold Chain Consultants onsite corrective actions were implemented and the resulting qualification of the same cool room.

Every year we find many cool rooms which fail to maintain temperature, incorrectly qualified and passed audits by numerous companies. We recommend using companies with experience in pharmaceutical qualification and refrigeration technical expertise when hiring contractors to perform qualification on facilities. It is important to properly qualify equipment within the supply chain, we generally experience the further down the supply chain from the manufacturing site the higher number of facility non-conformances. With the EU GDP guidelines Clause 7.2 stating the Contract giver must ensure the contract receiver is complaint, their cannot be any risk with facility qualifications.

Qualification of temperature controlled environments requires the extensive knowledge of the operation of the equipment. However the corrective actions required to balance and correct poor performing facilities requires a greater depth of technical knowledge and experience. Some of the root causes we have found are the refrigeration technician's lack of experience in pharmaceutical qualification requirements, along with poor installation, lowest price purchase of equipment and substandard original design specification not meeting the operational requirements.

RISK MANAGEMENT GOVERNANCE

In the past few years we have all felt the impact of natural disasters and in the global temperature sensitive supply chain including recent events in the USA, winter storms, flooding in the UK, and other tragic events across the globe including the recent Ebola outbreak. The key message here is to ensure your supply chain is supported with current risk management practices and processes, including business continuity plans are in place, reviewed at least annually and tested.

SUPPLY CHAIN SECURITY

This topic is now gaining more awareness within the industry and is a key link within our supply chains, the recent introduction of physical security initiatives in the USA and Europe via a number of collaborative working groups and education forums have seen a reductions of events.

CCC have conducted gap audits which have identified supply chain security breaches , and have assisted our customers to implement a higher level of security procedures for our customer's supply chains and we advise this is a key focus for regulators as it directly impacts patient safety.

Counterfeit products are still a concern for the industry, the current global serialization initiatives being rolled out shall allow in the near future, product traceability from the plant gate to the customer which in turn will complement the quality compliance of medicinal products across the supply chain.

SUSTAINABILITY

From our recent observations the topic of sustainability within the temperature sensitive supply chain tends to waiver in and out of focus, it should be noted that a good sustainability strategy can have significant impact on your supply chain optimization. In Lean terms there maybe waste and extra costs that you are not aware of, our message here is, that it always worthwhile to conduct an annual check of your current strategy and operational process to ensure best practised is maintained.

THE LAST MILE

During inspections the qualification of the CRT and cold chain last mile is being questioned in more detail in many countries. We are also observing the end customers are now starting to request qualification information from wholesales and 3PL for deliveries to their sites. It recent months contracts to supply hospitals and clinics have been lost due to no documented or poor qualification of the last mile temperature supply chain.

We expect in2015 this trend will increase as the every Hospital and Clinic is being more informed about the temperature supply chain and requirements of EU GDP guidelines rapidly spread worldwide. Even though the EU Guidelines are not enforceable in many countries the industry is enforcing them as a part of their risk assessment of suppliers and when reviewing their risk of the lifecycle of the product across the world. Insurance companies are also now using the guidelines to assess their risk. You should not be complacent as its not just regulatory inspections forcing change in the industry. The cost of losing a major supply contract is much higher than the cost of compliance.

CLINICAL TRIALS

With the trendof clinical trials moving to emerging markets in an effort to reduce costs, these markets do require more rigorous qualification and strong enforcement of processes within the supply chain.

A recent GAP audit conducted by CCC identified a large percentage of products were being frozen in the supply chain when the 2-8ºC products were being shipped with Dry Ice at -70ºC , despite an abundance of ice packs being available onsite. (This is not the first time we have witnessed this and we felt worth bring to companies attention as it is quite common.) There is often limited knowledge and training and the general view in many markets is cold chain product must arrive at the site cold. The complaints they received were about warm product arriving at destination. When they couldn't pack anymore frozen ice packs into the packaging they found using dry ice stopped the complaints and the products arrive cold. The cost of the dry ice was also lower cost than using the large quantity of Ice packs.

The emerging markets will focus on the most cost effective method of achieving the shipment which can comprises the quality focus. , It is common for CCC to find that the actual process which was audited and verified is very often only utilised at the time of the audit and ignored in standard operational shipments.

We often have internal discussions on the real costs of poor supply chain practices in clinical trials temperature supply chains, which might prevent drugs from continuing to next stage. Again we note the further down the supply chain from the sponsor, the more we identify significant temperature excursions and poor practices, and not only in emerging markets.

With more new biological products being developed the importance of a qualified robust clinical trials temperature supply chain is required to achieve the best results from the studies.

TRANSFERENCE TO 3PL'S *'DOESN'T AVOID RESPONSIBILITY BY CONTRACT GIVER AND RECEIVER'*

The outsourcing trend has changed from selecting the successful tenderer on prices then handing over to the quality department to review compliance from a selection of providers. To the surprise of many un-successful tenderers they have not passed the first round of the pre tender processes and provided with the opportunity to submit a price.

CCC advice to 3PL and 4PL providers is that you must be prepared for the pre tender inspections or you will not be invited to tender. The quality departments will be closely reviewing and looking for the poor practices and substandard systems including major GAPS and Risks in your supply chain.

The QA departments are more accountable for supplier inspections and they want to reduce their own risks and workloads. Every excursion or adverse event will require a review by the QA department and their resources are often already under high workloads and time pressure.

COST EFFECTIVE PACKAGING SOLUTIONS

At all the cold chain conferences, we've attended across the globe for the past 10 years, we hear the same requests, "We are looking for cost effective packaging solutions". We always ask of these people the question "what do you mean by cost effective?" To which often we get blank looks.

If you can answer the question on what is the requirements of "cost effective" then you are on the way to finding the solution. Cost effective in terms of purchase price, minimising costs of temperature excursions, cost effective total supply chain, cost of failing an inspection, cost of a legal cases, if the delivery of a product is proven out of specification or the cost of losing a major contract.

With a focus on the temperature sensitive supply chain these questions are important to ask internally as a part of the risk assessment. A cost effective solution can only be achieved by optimisation of the supply chain and balancing all the components against the end to end cost and the risk.

We need to be reminded that cold chain packaging is all based on physics. For hundreds of years no one has been able to refute the Laws of Physics we all learnt at school and you can't cheat physics. I assure you at CCC we are constantly reminded of the laws of physics many times over with every testing failure when designing and qualifying packaging for some of the industry's most difficult problems.

One of the most notable reminders being, we added extra gel packs to increase the qualification time only to find the time was reduced. A law of physics we had neglected to consider, and the laws of physics had won again. Anyone who can explain this fully understands thermal packaging!

FINDING A CONSULTANT

We are often asked the question who would you recommend for a particular project and even more often how do we identify if you are the right consultant. How do we choose between your company and another?

To help you find the right consultant we recommend the following process:
Firstly, write a detailed scope of works .We receive many invitations each year to tender for work and often the scope of works are very limited in details and the deliverables are not clearly defined. A well-defined scope of works with project justification will need to be identified, as well as project requirements, milestones, and deliverables. Any non-goals or items that fall outside of the scope of the project need to be identified. The necessary, deliverables need to be tied to specific milestones in the project schedule. The more detailed and better prepared the scope of works the more successful you will be in finding the right consultant.

One important method of determining a consultant's level of knowledge is to gauge the questions on each deliverable from the tenderers in the Q and A. These will provide insight into their knowledge, experience and skills. This will only be useful if the scope of works is well structured and detailed.

FINDING A CONSULTANT

The second point is to request information on the types and variety of projects they have conducted. Temperature supply chain is very complex and all elements are interconnected and lead to supply chain success or failure. The wider the experience, the more knowledge they will bring to the company or project which will translate into shorter timelines and reduced costs. Often the tenders are released by a purchasing department whose knowledge of temperature supply chain is limited and we recommend to engage the logistics team to structure the scope of works for the purchasing department.

If the expertise are not within the company then "You don't know what you don't know" and it is now very common practice for companies to engage consultants to write scope of works for a project. They can structure the scope using the correct terminologies and identify the deliverables really required. This does not guarantee they get the job and they should not be given any preferential treatment in the tender process. They are engaged just to prepare the scope of works.

A good consultant can identify the needs for the scope within a 1 or 2 hour meeting in person or web meeting and write a scope of works within a few hours. A review by the company's project team, a second meeting and the scope of works should be finalised and ready for release.

A considerable amount of our work over the past year was dedicated to administrative type roles where we assisted Pharmaceutical companies prepare tender documents to engage 3PLs and reviewed the 3PL submissions for GDP compliance.

Other projects included developing project plans for companies with limited temperature supply chain resources, develop project plans and strategies which they could manage internally. On the other side we reviewed many 3PL tender submissions for documentation accuracy and GDP compliance as long as there was not a conflict of interest.

The role of a temperature supply chain consultant is quite varied. Cold Chain Consultants specialises only in pharmaceutical temperature supply chain. The information we have provided is of a general nature and summarised from our observations within the industry. It is not intended as specific advice or as the only solution to problems.

We trust our annual report it is of benefit in providing some insight into activities and future direction as we see it in the pharmaceutical temperature supply chain across the world.