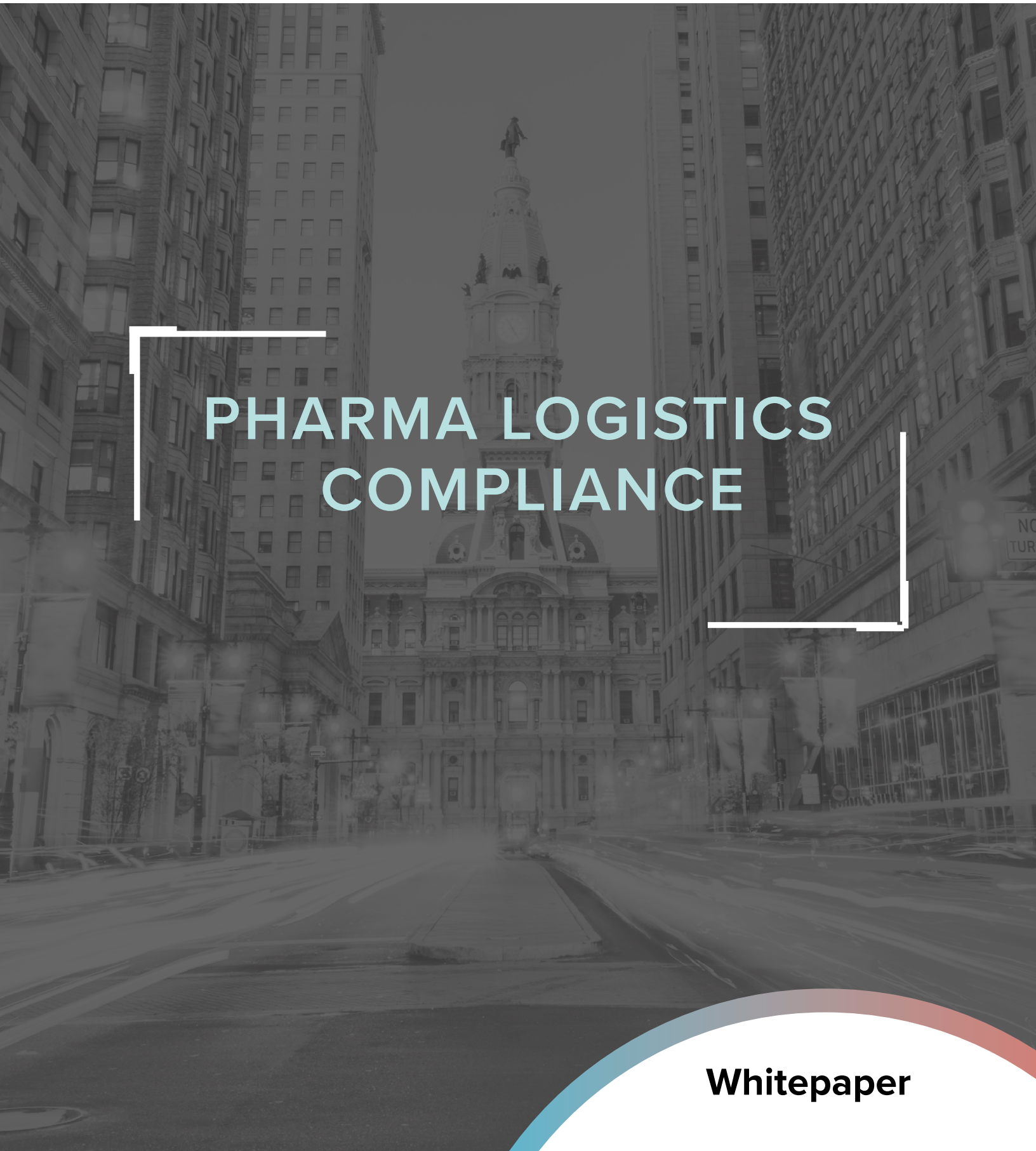
Cold Chain Global Forum CANADA . 19
Temperature Controlled Life Science Supply Chains

Pharma Logistics IQ



PHARMA LOGISTICS COMPLIANCE

Whitepaper

Pharma Logistics Compliance

Rising expectations from the world's regulators have undoubtedly developed the quality of the supply chains transporting today's medicines. Pharma logistics has matured greatly from the days of being left as a last minute consideration within drug discovery and production.

Last year, saw a lot of progression from regulators. In January, Australia's TGA enforced new manufacturing requirements. The authority is phasing its on-site inspections for the new standards. By this summer, manufacturers should have assessed how the principles will impact operations, this should include updates to quality system documentation. Manufacturers will need to have adequate justifications for their lack of progress if they are unable to meet the Summer's deadline.

The end of 2017 saw the **MHRA publish its latest GDP deficiency data.** Of the 1420 that inspections took place in 2016, quality systems and transportation emerged as the top categories for major deficiencies.
One deficiency citation relating to Responsible Person requirements noted a holder had not nominated a responsible person with sufficient knowledge of activities. "The RP was unaware of how additional requirements imposed on certain products by national law would be adhered to, for example, the MHRA published guidance on export that related to 'controls on strategic goods and drugs used in execution by lethal injection'."

According to some of the quality management citations, change control was not adequately detailed in some cases. Also, there was no formal process for the review of outsourced activities or written procedure outlining the due diligence arrangements for qualifying contractors.

In regards to transportation, some of the MHRA's citations included:

- Lacking temperature mapping for storage areas regarding the placement of monitors.
- Temperature deviations being recorded but not undergoing CAPA reporting.
- Incorrect thermometer calibration.
- Gaps in contemporaneous temperature records.

Session Spotlight

KEYNOTE: Global Regulatory Compliance Panel: How can we Ensure we are Compliant with all Regulatory Agencies Requirements?

Belgium's Federal Agency for Medicines and Health products (FAMHP) alerted authorization holders to adhere to their new packaging and labelling guidelines. The modifications were made to better align with other international requirements.

The main changes related to the packaging text as per the QRD template, the use of logos, QR codes, the definition of small packages and the submission of mock-ups.

Medical authorities plan to keep advancing the quality and security of supply chains transporting medicines. Therefore, medicine manufacturers and authorization holders must keep updated with the latest developments and the key points predicted to shape the compliance agenda for 2018.

Session Spotlight

Understanding Global Inspection & Audit Observations for the Implementation of GDP in order to fix Vulnerabilities

Rafik Bishara Ph.D.
Technical Advisor & Former Director QKMTS
Eli Lilly & Company

Supply Chain Security and Traceability - GPS

As mentioned by **Authentix** in a recent whitepaper, counterfeiters enter the legitimate supply chain – it's not a matter of if, but when.

Granted counterfeit pharmaceuticals are more frequent in developing markets. However, the counterfeit pharmaceutical industry is worth over $75 billion annually, according to Interpol.

In a case earlier this year, the medical regulator for Nigeria alerted that fake Coartem tablets had entered circulation. The manufacturer's name on the fake tablets was listed as NOVRTS. The regulatory body noted: "The use of fake Coartem tablets may result in poisoning (due to toxic substances), treatment failure, development of resistance and even death."

What's being done:

Several supply chain security solutions are available for manufacturers to deploy:

- Overt security features and inks on packaging
- Covert machine-readable inks and taggants preferably with read-through packaging detection
- Tamper evidence indicators
- Serialization tracking and GPS traceability.
- The industry is preparing for a range of serialization regulation deadlines across the globe.

The **EU recently published a report** detailing the implementation of the Falsified Medicines Directive (FMD). The majority of EU member states have introduced penalties for breaching FMD law.
These vary from imprisonment, fines and administrative sanctions - the maximum prison sentence is three years.

As the subject is very close to his heart, Rafik Bishara, Ph.D, former Director QKMTS, Eli Lilly and Company urges the industry to pay attention to securing the pharmaceutical temperature controlled supply chain – to guard against theft, loss, diversions, tampering and the introduction of counterfeit products.

To be assured that the inspected manufacturer has done everything possible to enhance the security of the supply chain, regulators and inspectors will ask to see risk analysis' and risk mitigation processes.

Rafik feels that security should be one of the first mitigation and analysis' to be conducted. "We have to pay attention not only to the security of the product as it's leaving the manufacturer, but [remember] cargo in a parked truck has a higher probability to be stolen versus a cargo that's on the road."

Truck drivers should know the route and they should not deviate from it, if a deviation is needed for a certain reason, dispatchers should be notified. If the driver must stop to rest, the truck needs to be parked under a well-lit parking spot and the cargo should be secured via a lock.

Rafik notes that manufacturers could use light sensitive devices as a security monitor to alert and intervene against any tampering activities.

Brexit

At the end of 2017, **fractures began to emerge within UK and EU supply chains** ahead of the trade hurdles to be caused by Brexit.

Surprisingly, almost one in ten of the supply chain managers surveyed in recent research admitted their business had lost contracts due to Brexit. Furthermore, 14% feared parts of their operations will not be viable any longer.

In the space of 6 months, the amount of EU businesses that expected to move some of their supply chain out of the UK due to Brexit jumped up to 63% of the practitioners surveyed.

Around 40% of UK businesses began looking for local partners to replace their current EU partners. Encouragingly however, 26% were determined to invest in strengthening relationships with their Europe based suppliers.

In order to minimize breakage, industry commentators have urged the British Government to strive to minimize tariffs and quotas between the UK and Europe in negotiations.

The deadlock in Brexit negotiations has flared uncertainty. However, at the end of last year, **the nation's medical regulator** clarified that it foresaw no sudden changes to compliance requirements as a result of Brexit.

Even though it is hard to predict the final outcome Rafik notes: "In summary, Brexit may have an effect. The most concern I personally have is to avoid the shortage of medicines and vaccines for the patients."

"It is going to be a challenge in that transition period as the UK starts implementing Brexit."

The majority of the big pharma manufacturers are global companies, they will need to know the conditions that must be met in the transition period so product can be imported into the UK or exported successfully.

He indicated that there are various organizations working to minimize the impact of Brexit and prevent a medicine or vaccine shortage. For example, with plans to overstock medicine.

ICH Q12 Flexibility Initiatives

After being discussed for a few years, regulators are now implementing ICH Q12 guidance – the technical and regulatory considerations for post approval change management.ICH Q12 will enable license holders to make changes post-approval of their product. Post Approval Change Management Protocol (PACMP) as suggested in ICH Q12 is an important tool to enhance supply chain flexibility.

What's going to happen in 2018?

There are five stages of ICH approval. The Q12 guidance is currently in the second stage and is under public consultation. The subsequent phase, is to finalize the document and get to the next level of adoption.

Ajay Pazhayattil, Former Associate Director, TOPV Apotex Inc. explains that 2018 will see the biopharmaceutical industry wanting additional clarity on harmonized filing categories for specific post approval changes. Also, standardization of PACMP will be a need so that it can be used routinely without any hesitation for all initial regulatory submissions.

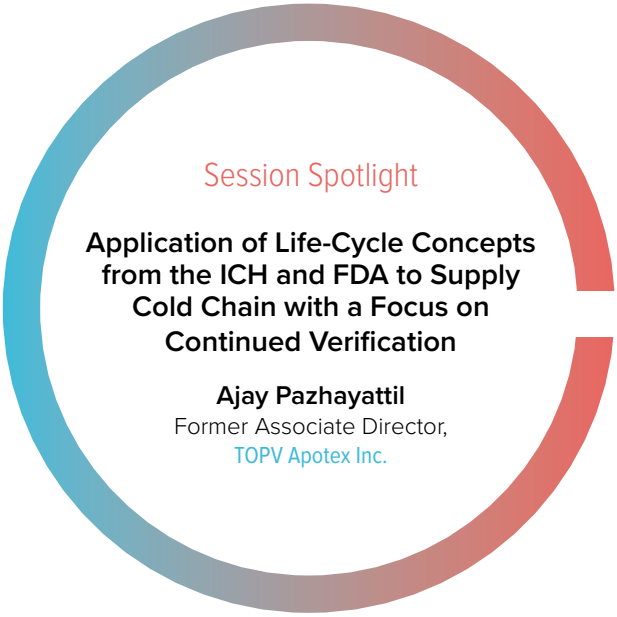
Major industry organizations, including the Parenteral Drug Association (PDA) and the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) are working towards addressing some of the post approval change challenges while applying ICH Q12 concepts.

Post-approval change management protocols (PACMP) provides with the anticipated changes that can potentially happen to a submitted product during its lifecycle. Ajay notes that the product license holder proposes the changes, the detail of the acceptance criteria and special commitments to be accepted for a reduced submission category.

Challenges ahead

To be successful in using ICH Q12 concepts; heightened product/process knowledge, effective risk management tools, continued process verification program and fit for purpose data driven statistical tools are essential. Firms utilizing contract manufacturing organization's (CMOs) therefore are expected to face hurdles in implementing the prerequisites. However, Ajay notes that as the benefits are understood, inevitably more organizations will adopt post approval change management strategies utilizing the ICH Q12 suggested tools.

The regulators themselves have challenges to overcome as the guidance presents a new territory. Ajay warns that inclusion of PACMP may likely cause extra delays for approvals during the initial stages. The regulatory bodies will have to handle the rising filings utilizing ICH Q12 elements, PACMP protocols. Large molecules are indeed the future with exponential growth needing faster development and continuous improvement. There are more than 200 approved biologics with many more in the pipeline. However, the unpredictability of post approval changes with biologics presents a challenge. Continuous improvement changes are critical for biologics products to ensure long term sustainability. More understanding is required to fully grasp the complex challenges associated with implementing ICH Q12, which will enable preventing supply disruptions down the road for biologics producers.



EMA Regulations

Manufacturers of Advanced Therapy Medicinal Products (ATMPs) have until May 2018 to comply to the **GMP** guidance adopted by the Commission on the 22nd of November of 2017.

The new document provides guidance tailored to the challenging manufacturing issues associated with ATMPs which feature gene or cell based materials for medicinal applications. These requirements relate to approved products and those in clinical trials.

The commission details that manufacturers need to take a quality focused, risk based approach to protect the integrity of finished products.

Quality reviews should be conducted annually to verify the consistency of processes and identify areas for improvement. More extensive reviews need to be conducted for product lines manufactured at higher volumes.

“The risk-based approach permits the manufacturer to design the organizational, technical and structural measures that are put in place to comply with GMP -and thus to ensure quality according to the specific risks of the product and the manufacturing process. “

Considerations factor in that the academic/ hospital settings where these products are developed and administered are very different to those sites used to produce conventional medical products.

The commission is aware that because of the complexity and diversity of ATMPs, the risks to quality are likely to differ from product to product. Also, each batch may contain variability due to the biological materials used and the manipulation steps in the manufacturing process, for example the cultivation of cells.

The authority continues: “In laying down the GMP requirements applicable to ATMPs, it is necessary to recognize a certain level of flexibility so that the ATMP manufacturer can implement the measures that are most appropriate having regard to specific characteristics of the manufacturing process and of the product.”

Access the GMPs for ATMPs guideline here

Clinical

This year, the clinical trial market will continue to prepare for the launch of the EU portal in line with the union’s new clinical trial regulations.

In June 2017, the European Medicines Agency management board announced that instead of launching in October 2018 “Due to technical difficulties with the development of the IT systems, the portal’s go-live date has to be postponed [to 2019].”

This announcement, along with some of the labelling requirements, have generated frustrations within the industry.

Some critics believe the labelling requirements restrict flexibility, decreasing the amount of supplies ready to be shipped to patients and upping the amount of update handling required.

The regulation depicts Investigational Medicinal Products (IMP) be appropriately labelled to ensure the subject’s safety and the reliability of data. It requires expiry or retest dates to be printed on both primary and secondary packaging, contrarily to the current period-of-use information visible on the outer packaging.

Steve Jacobs, Chair, Global Clinical Supplies Group said: “Clinical trial regulation expects us to put expiry dating on almost everything, all the way down to primary packaging. In some cases even five milliliter vials come under consideration by some regulators.

“The key to this whole thing is that labelling requirements are a nightmare. If we actually find ourselves having to update expiry dates, we would almost have to open the clinical packaging to do it which causes a bigger nightmare from a quality perspective.

FDA

The FDA is to publish **98 draft guidance documents** in 2018. Two are listed under pharmaceutical quality manufacturing standards, with one guidance focusing on Human Drug Compounding Outsourcing Facilities.

After delaying the enforcement date as many in the market hadn't installed the technologies or capabilities required, especially small to mid-sized manufacturers and CMOs, pharma companies will have until November this year to comply to the **US Drug Supply Chain Security Act (DSCSA)** requirements

Regarding medicine distribution compliance, the EU GDP is the leading document referred to by the European regulators. Rafik says "at the moment the FDA does not have a good distribution practice document, but they rely that the good manufacturing practice, until it reaches the patient, includes the good distribution practice." So global pharma manufacturers in the US need to be familiar the EU GDP requirements.

Several of the United States Pharmacopeia chapters (<1079>, <1118>,<659>) give manufacturers operating in the US and globally the direction needed regarding the handling, storage and distribution of medicines.

Emerging Markets and GDP

Rafik noted that there is an awareness in the emerging markets of what the current best practices are. “In March 2018, I was chairing a conference in Hong Kong and I am pleased to report that in that conference, the Hong Kong International Airport met the IATA CEIV certification, which again incorporates many of those standards.

“Several of the speakers discussed topics such as what is the storage temperature, what are the shipping temperatures?”. Lane qualification was also addressed.

He added that some developing countries, and the companies that operate within these regions, are doing their best to meet requirements and are getting there.

Recent progression

Brazil: ANVISA recently released a new regulation expected to transform the nation’s GMP inspection and certification measures.

India: Recent reports emerged stating the Drug Controller General of India (DCGI) may blacklist multiple Chinese API firms.

China: China and the UK finalized a memorandum of understanding in an effort to solidify international relationships to strengthen medical regulatory systems. In 2016 **China’s Food and Drug Administration (CFDA)** cracked down on illegal medicine distribution behavior by issuing a round of unannounced inspections on wholesalers.

In the same year the CFDA conducted over 430 pharma inspections, which saw over 50% of the drug manufacturers disappoint expectations

Nigeria: In January and February the **National Agency for Food and Drug Administration** and Control (NAFDAC) confiscated over 40 container loads of drug substances. The controlled drugs, mostly Tramadol, were seized at a range of seaports across the country.

Pakistan: Over the last three years, the **Drug Regulatory Authority of Pakistan (DRAP)** initiated the testing of 171,000 samples at laboratories in its campaign against spurious drugs.

Last year, the authority launched 1,452 drug court cases within a nine month period, 884 reached decisions of which eight drug manufacturing licenses were suspended/cancelled.

The same period saw 784 GMP inspections take place.

Those that are not up to par in emerging regions have been known to receive citations from various global regulatory inspectors. These citations have occurred in the area of finished products, as well, active pharmaceutical ingredients.

International Collaboration

Globe's regulators do communicate and collaborate to ensure audits and inspections follow current best practices. For example, in a move to conserve inspection resources and avoid duplication, the **US FDA** has extended permission to four EU states – Czech Republic, Greece, Hungary and Romania to conduct FDA level GMP inspections by July 2019.

Rather than there being a difference between EU and American inspections, Rafik suggests that it is more about inspector dependent differences. One of the very tough issues faced with this concept is the subject of storage temperature in relation to transportation temperature.

Rafik said: "Some inspectors would say they should be the same; other inspectors will work with the industry if you have stability data to allow some excursions as long as the product is stable." With CRT medicines regulators and inspectors are starting to ask for evidence of control during storage and transport, 'Show me the data that this product has been stored and shipped under proper conditions?'

Points to remember for your next GDP inspection

1. Documentation, documentation, documentation: "If it's not written, it didn't happen."
2. If you have an SOP, follow it: As an inspector, if they find that you have an SOP and you did not follow it, that's even worse than not having an SOP.
3. So you've gathered data, but what did you actually do with it? If there is a deviation on excursion, what is the investigation? How did you correct it? Have you initiated CAPA (corrective action, preventive action) to prevent it from happening again?

Learn More!

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Temperature Controlled Life Science Supply Chains

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