pci PHARMA SERVICES

EU GDP Guidelines: Implications for Shipping Clinical Materials into the European Market

pci CLINICAL SERVICES

EXCELLENCE IN PHARMACEUTICAL OUTSOURCING FROM MOLECULE TO MARKET

Recently, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) opened an investigation into a patient complaint of mold on paracetamol (acetaminophen) tablets.[1] It discovered the product was shipped by sea from India to multiple companies in the UK at temperatures reaching up to 60 degrees Celsius. Labeling for paracetamol tablets typically states they should be kept below 30 degrees Celsius. In addition, MHRA discovered the humidity levels exceeded 80 percent during shipping, which is too high for the packaging that was used.

These excursions impacted the drug's ability to maintain the stability and quality intended by the manufacturer. As a result, MHRA ordered a recall of four shipping containers, which included over 100 batches of drug product. Because the company arranging these shipments had failed to follow the recommended practices outlined in the EU Good Distribution Practice (GDP) guidelines, the mistake not only cost it time and money but it also put the future of any company receiving the product at risk.

It is up to pharmaceutical companies sponsoring clinical trials in the EU to have comprehensive control of their supply chain. This ensures the quality of their drug supply is not compromised and patients are not inadvertently administered counterfeit or falsified drugs. The intent of the original EU GDP Guidelines created in 1994 was to encourage the safety and security of the pharmaceutical supply chain and outline the standards expected by EU countries and those trading with the EU. While the guidance was focused on commercial products, it is considered best practice for clinical trial shipments. It also helps prepare companies for what is expected when a product is approved for commercial marketing.

"The EU GDP Guidelines detail pharmaceutical supply chain safety and security standards that companies are expected to abide by. While focused on commercial products, these guidelines are considered best practice for clinical trial shipments."

As a result of the Falsified Medicines Directive and the increased threat of falsified medicines entering the legitimate supply chain, significant changes were made to the EU GDP guidelines in 2013. These changes also took into account the globalization of pharmaceuticals and supply chain complexity. The updates included several new sections as well as additional details in some existing ones, such as qualification and validation, risk management, and quality management. Many sections within it now align more closely with GMP expectations. The new guidelines also offer more comprehensive guidance for temperature management during storage and transportation.

Quick tip

We recommend sponsor companies generate stability data for their development drug for varying times and temperatures outside of the expected ranges. If the temperature recorded goes slightly outside of the required range during storage/transportation, sponsor companies may be able to use the stability data as supporting information to show the drug will still have its intended therapeutic effect. Once a product arrives in the EU, it will not be certified for release by a Qualified Person (i.e., the person who legally certifies materials coming in from outside the region) until they are convinced the transportation and storage conditions requirements have been met. If there is a temperature excursion and the sponsor company can provide stability data to support it, the product should be suitable for release. If not, the Qualified Person will have no other choice than to reject the shipment.

A focus on drug stability and security

Maintaining product quality and integrity is increasingly difficult in today's industry. In recent years, there has been explosive growth in the biotech and advanced therapeutics markets. This makes the need to maintain appropriate temperature and environmental conditions for these sensitive drugs a major focus.

Should a batch of drugs deviate from its required temperature range during storage and transport, it may not be able to provide its intended therapeutic effect. This risk becomes even higher if a drug is temperature sensitive and has to travel through changing or extreme climates.

The growth of counterfeit drugs and/or falsified medicines in today's market is staggering. In the EU alone, counterfeit medicines were part of the top five products confiscated in 2016.[2] These breaches present financial risks to a company and can inflict lasting damage to a company's brand reputation and bottom line. Even more importantly, they can hurt or even kill patients.

To avoid quality, security, and compliance risks, sponsor companies must be responsible and accountable for knowing the transit history of their clinical materials, even if they hire a partner to manage distribution. It is imperative to know whether a partner's supply chain counterparts also take appropriate security measures to prevent penetration of falsified drugs. For anyone considering entry into the European market, the updated EU GDP guidelines make several recommendations that can address these risks and even more.

RECENT EU GDP CHANGES YOU NEED TO KNOW

The expanded oversight from the updated EU GDP guidelines brings nearly all finished pharmaceutical products under these temperature control requirements during transit.[3] With this in mind, it is critical for the industry to understand and follow them.

Although sponsor companies should be familiar with the guidance in its entirety, particular focus should be on these three areas:

1. Quality Systems

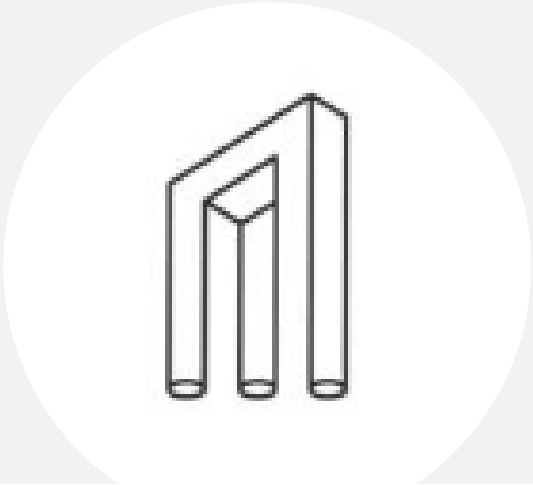
A quality system for distribution manages vital information, such as: deviation investigation and CAPA, complaint handling and recall process, controlling storage areas to be GMP compliant, and controlling environmental conditions during transportation. The 2013 changes in this section of the GDP guidelines indicate a sponsor company must have a comprehensive quality system in place and not just a series of documents without any underlying system that ensures they relate to each other for all aspects of storage and transportation.

Full documentation must be available, and traceability of all products must be possible while the product is in storage and/or during transportation. The sponsor company must also be able to ensure the specified temperature conditions for that product were maintained during the transportation process and that records are available to verify this. In other words, sponsor companies need to ensure they have sufficient oversight of the whole process and that they are informed if there is a temperature excursion at any stage throughout this process. As a sponsor company, do your quality systems tell you your distribution handoffs along your entire supply chain?

The sponsor must be able to provide any information requested by the EU Qualified Person (QP) (i.e., the person who legally certifies materials coming in from outside the region) regarding storage and transportation, including routes and companies used, and temperature records demonstrating the product was held in appropriate conditions during this period. Remember, this might not be only temperature control; it could include other aspects, such as humidity control and avoidance of light, vibration/shock, and dramatic pressure changes during transportation (e.g., for prefilled syringes). To provide a robust system, sponsors should always consider the use of at least two data loggers, which measure and record product temperatures during shipment and can often provide the QP with the information they require. Depending on the size of shipment, the number of data loggers may need to be increased significantly.

Quick tip

Use source loggers that are easy for the site to read/interpret and provide a simple worksheet for them to complete that captures conditions during shipment.



Change your perspective

Do your clinical sites know what to do with the physical temperature monitors upon receipt? It is not uncommon for clinical sites to receive temperature-controlled supplies without instructions on how to handle the physical temperature monitors. This can lead to the loss of data and may prevent use of your trial product.

2. Equipment

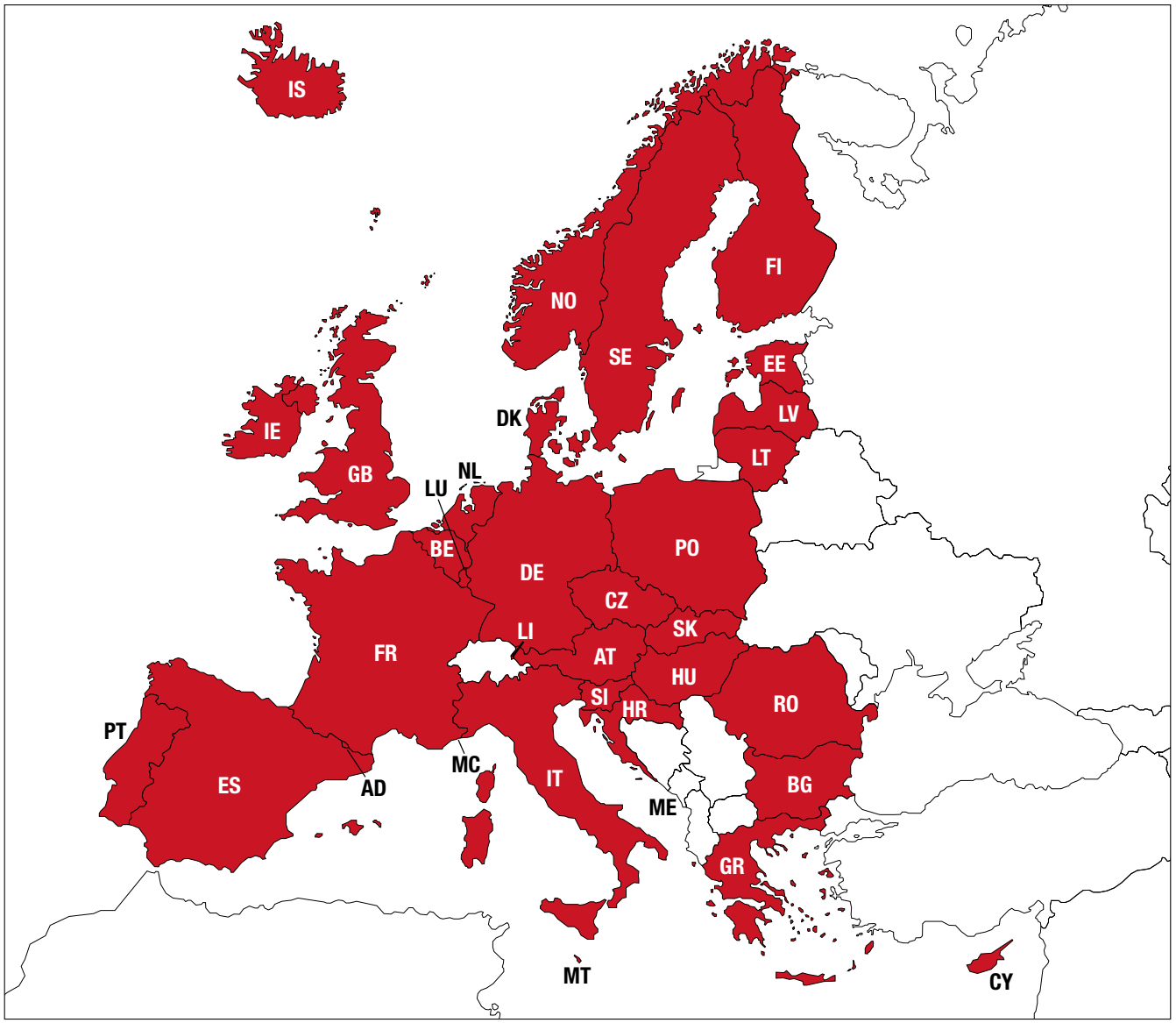
Any equipment used for the transportation and storage of all drugs, including those that are temperature-sensitive, should be "designed, located, and maintained to a standard which suits its intended purpose." All drugs must be kept within their stated temperature storage conditions. This requires the use of validated packages/shippers, and validated temperature-controlled trucks, refrigerators, and/or freezers.

For clinical trials, it is commonly accepted practice to use prequalified shippers. Remember, this should include those drugs that must be stored below 25 to 30 degrees Celsius, not just "temperature-sensitive" products. The equipment must also be able to control other specific conditions as needed, such as humidity, lighting, etc.

It is important for sponsor companies to understand the difference between qualification and validation, as these are referred to frequently in the GDP guidelines:

- Qualification refers to the quality of the equipment and indicates it has been tested under standard, highly-controlled conditions (i.e., prequalified shippers). Therefore, it is important that any data loggers used are certified (qualified) and come with a calibration certificate or equivalent. For shippers that state they have been qualified for a number of hours (e.g., 72, 96, or 120), the sponsor should request formal documentation from the supplier that demonstrates the packaging complies with the stated specification.
- Validation refers to the quality of the process. Equipment has been validated only after it has been tested by simulating actual payloads and transport temperature profiles.

31 Countries follow the EU GDP Guidelines



3. Computerized Systems

To document and manage data from temperature-controlled shipments, a system that is "capable of achieving the desired results accurately, consistently, and reproducibly" is recommended. Written documentation must be available explaining how the system works and how it interacts with other systems. Sponsor companies and their partners should also use a risk assessment approach to determine which qualification and/or validation activities will be used to ensure equipment is correctly installed and operated. This is especially important if shipments are of high value or in limited supply, as is often the case for clinical trial materials.

Any information captured during shipment should be:

- Entered into the computerized system only by authorized personnel
- Secured physically or electronically and protected against any modifications
- Backed up regularly
- Stored at a separate and secure location for at least five years or longer, depending on local regulation requirements

From a clinical trial perspective, a sponsor company will face queries about temperature and storage conditions upon its materials' arrival in the EU, just as it would with commercial materials. A QP overseeing the shipment looks for this

information to ensure the transportation conditions were suitable for the product in question. A company can avoid delays and costs associated with rejected material by using data loggers in its shippers.

There are currently 28 countries in the EU following these guidelines, with each country potentially having its own nuances in the regulations. In addition, Norway, Iceland, and Liechtenstein also abide by this guidance. Early engagement with a clinical packaging partner could provide you with the expertise and understanding needed to successfully ship your materials into each of these countries. However, among other critical requirements, you must select a clinical packaging partner that:

- Is familiar with temperature-controlled packages
- Is experienced with shipping to a large number of countries, including the EU
- Understands the requirements of the EU QP
- Possesses expertise in documentation requirements

Partnering with a company capable of overseeing the safety of your supply chain with knowledge and experience gives you the resources you need to ensure effective and efficient support of your clinical trials. In a growing and changing global market, the value of that kind of expertise is immeasurable.

References

[1] Indian-made Medicines Including Superdrugs Ibuprofen Recalled by UK Health Regulator – http://www.independent.co.uk/life-style/health-and-families/health-news/ indian-made-medicines-including-superdrugs-ibuprofen-recalled-by-uk-health- regulator-8886759.html

[2] European Commission, Report on EU customs enforcement of intellectual property rights: Results at the EU border, 2015 – https://ec.europa.eu/taxation_customs/sites/taxation/files/2016_ipr_statistics.pdf

[3] Zuellig Pharma, A Spotlight on Temperature Management – https://www.zuelligpharma. com/insights/a-spotlight-on-temperature-management

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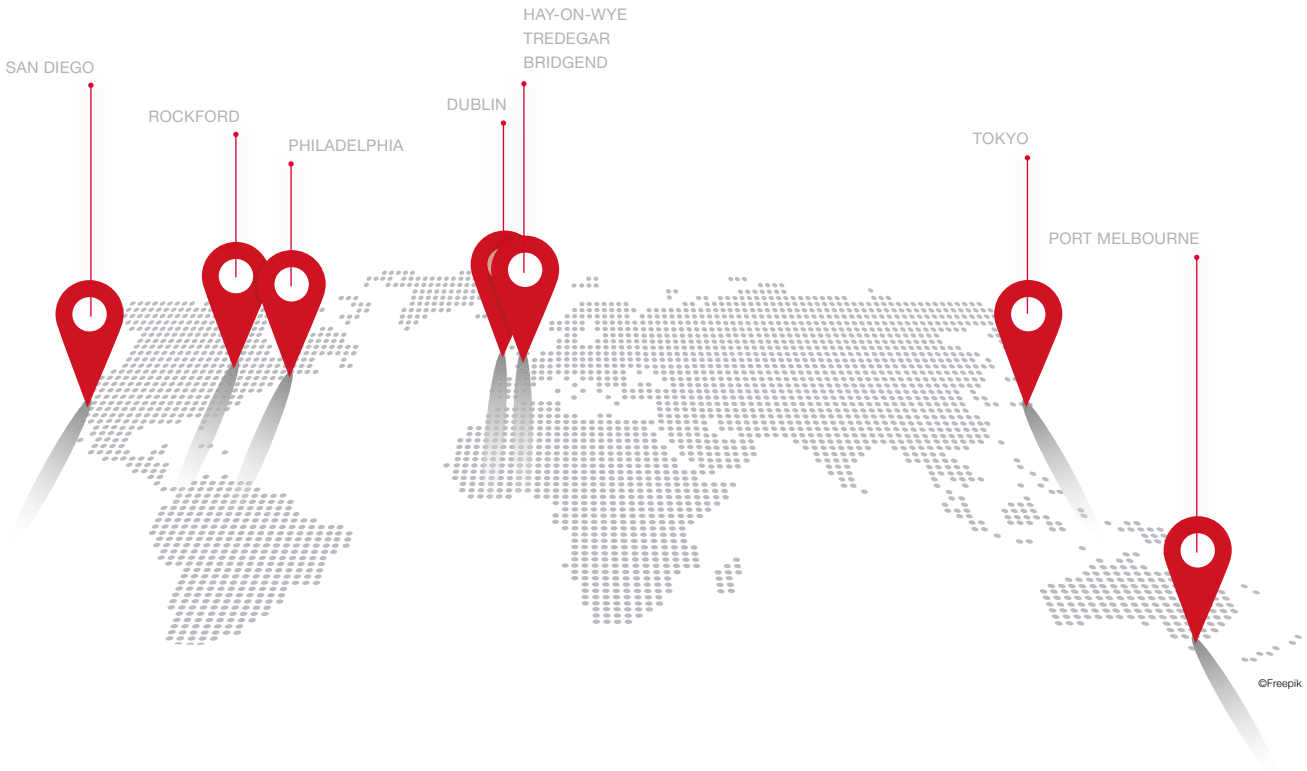

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e : sales@pciservices.com **w : pciservices.com**

NORTH AMERICA

PHILADELPHIA: +1 215 613 3600 | ROCKFORD: +1 815 484 8900 | SAN DIEGO: +1 858 997 1490

EUROPE

HAY-ON-WYE: +44 (0)1497 820829 | TREDEGAR: +44 (0)1495 711222 | BRIDGEND: +44 (0)1656 750550 | DUBLIN: +353 1 841 8300

ASIA PACIFIC

TOKYO: +44 (0)1495 711222 | PORT MELBOURNE: +61 3 9673 1000