

Is It Worth the Risk without Temperature Monitoring?

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Introduction

Temperature-sensitive medicinal products deliver unique value to the end-user while introducing several logistical risks to the shipper. How can the pre-qualified shipper ensure the product remains within the specified temperature range? What document proof exists that the temperature was maintained for that specific shipment on that route under those ambient temperatures with the many handlers that move the shipment from point A to point B?

Although designed to perform for a pre-determined time period at a given temperature range, a pre-qualified shipping container *may not always perform properly*. In fact, the shipper could experience significant temperature deviations without being detected.

Some reasons why a pre-qualified shipping container does not perform properly:

- Container was not assembled correctly – human error
- Product was not pre-conditioned properly
- Coolants were not pre-conditioned properly
- The external temperature exceeded design limits of the container

These temperature excursions would have gone unnoticed if a temperature monitoring device had not been utilized.

This article discusses the value of temperature monitoring and illustrates the point that a pre-qualified shipping container is only part of the solution to temperature control during transport. The reason why a temperature monitor should be used for each and every shipment of product will be proven by the costs and benefits, damage mitigation, process control, and regulatory compliance.

Advances in technology and growth of the market have made temperature monitoring accessible at a reasonable cost.

Since the risk of being outside the specified temperature range exists, monitoring should be considered when:

- Stability data on product is not adequate
- Controls and training are not in place for proper assembly of containers
- Events are unknown and there are no other means to detect shipping excursions
- Shipping lanes involve multiple handling and pose problems with: wrong orientation (container on its side), excessive vibration, shock, pressure and extreme temperature

Without a doubt, an industrial refrigerator containing medicines in a facility is a more stable environment, yet the refrigerator is monitored continuously and the record of events is recorded. Likewise, the chain of events for shipping should be recorded and documented to prove the product temperature was or was not maintained within limits. If limits are exceeded, armed with this data and other product information, Quality Assurance can determine if the product is acceptable. The temperature monitor designed for these cGMP requirements delivers the necessary records and documentation.

Technology

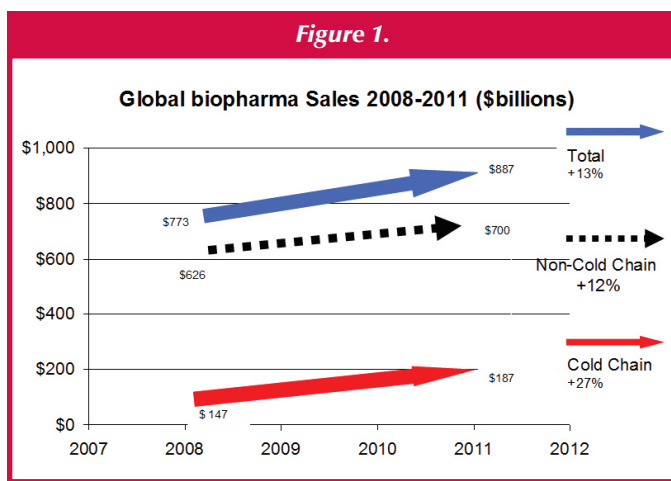
Before 2000

- Few temperature-sensitive shippers were pre-qualified
- Temperature dataloggers were expensive with few suppliers and little data capabilities
- Chemical indicators (not capable of being validated) were in wide use
- Regulations on temperature-sensitive shipping were being discussed as a concern, anticipating the guidelines in the future

See glossary for terms

Onset of 2010

- The term ‘shipping qualification’ becomes widely used. Shipping is not a validated process. Too many variables exist that complicate the process.
- Regulatory inspections and audits focus on shipping
- Many more shipping containers are pre-qualified and reliable
- Temperature monitors have improved accuracy with added features at lower cost
- Databases are moving towards merging current data about temperature and logistics of shipment
- Healthy competition exists among many suppliers in cold chain packaging and temperature-monitoring field
- New distribution strategies have direct shipments from manufacturers and healthcare companies to patients, physicians, and hospitals. This is a major shift as logistics will become more difficult



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Why is this Important? – Growth!

Not only is cold chain growing at a rapid rate due to the Biotech market, but increased concern for temperature maintenance in transit for all products, including controlled room temperature (CRT) products and the growth of biosimilar market (biogenerics), will continue to force temperature-sensitive logistics into the forefront. Cold chain biopharma products are projected to grow over 27% between 2008 and 2011, faster than global biopharma sales and non-cold chain as a whole. The majority of products in these categories require specialized packaging and temperature monitoring. By 2015, these products will comprise more than a third of all pharmaceutical products. This heightens the need for regulations to be harmonized worldwide with specific direction for the safety and quality of shipments. This may also be a major area of regulatory compliance and training for pharmaceutical companies.

Shipping – A Dynamic Activity

Shipping is a dynamic activity that involves the handling of the shipping container by multiple entities not controlled by the sender nor any single party along the shipping lane. The uncertain activities often outnumber the controlled activities of the shipping lane. The levels of service by carriers and couriers are designed to reduce the variability of the shipping lane beyond the shipping container. Factors such as weather,

long custom delays or inspection of the internal product by security, make the specialized cold chain shipment prone to the occurrence of mishaps along the way. Shipping is a fluid, dynamic activity that is difficult to control even if all the variables could be identified.

Why Monitor Temperature?

Temperature is arguably the most important environmental condition potentially affecting pharmaceutical products. U.S Pharmacopeia (USP) general Guidance Chapter <1079> “Good Storage and Shipping Practices” states: “Unlike shock, vibration, and other physical hazards, thermal hazards tend to be unique to a given system.” As such, it is critical to understand the unique thermal variability that exists in a given distribution environment or trade lane. Temperature is detailed on the product label and/or storage specifications and pharmacist instructions. Previously the emphasis was on cold chain (2°C to 8°C) and special packaging to provide the protected environment for the product. In recent years, regulatory agencies have added CRT product to their observations based on the temperature specified on the product label/ package insert(s). Shipping studies have revealed that the existing packaging and processes do not always deliver the product within the CRT range.

If label directions are not followed:

- Product is deemed adulterated unless such excursions are supported by stability data and associated thermal variability is appropriately documented
- Efficacy of product could be in question and clinical data may not be acceptable
- Procedures/processes may not be under control and corrective actions may be viewed as non-existent
- Storage conditions are out of compliance

Regulations and Guidelines

Temperature monitors help minimize risk. Regulators and investigators’ notes are clear on expectations.... they expect temperature monitors for each shipment.

Over the last ten years, regulations, guidance, standards and processes for cold chain have evolved significantly. However, enforcement has been approached differently from region to region. There is still a need to harmonize requirements and expectations for all temperature-sensitive medicinal products.

Temperature monitoring is currently required in Argentina, Mexico, Romania, Saudi Arabia, and in Ireland for large volume shipments. In the EU, temperature monitoring is strongly encouraged for other shipments. The EU GDP guidelines (document 94/C63/03) explain that drugs are expected to be held at the right condition at all times throughout storage and transport. It also establishes that a quality system is to be in place to ensure that the distributor, as well as the manufacturer, is responsible for this activity.

In the US, no laws are specific to cold chain logistics. However, the FDA has accepted GMP conditions during “holding” to include transportation (shipping) and distribution. Historically, the FDA has followed the EU in the area of cold chain.

When Temperature Monitors are not Utilized, There is a:

- Risk of not detecting temperatures, negatively impacting product efficacy
- Risk of corrupt or inaccurate clinical data
- Risk of losing product shipped and no documentation for insurance claims in determining liability

- Risk of losing credibility with investigators and/or distributors
- Risk of increasing costs due to replacement of additional product, freight, labor and extended timelines

Temperature-sensitive products should have procedures, packaging and temperature monitoring devices in place during shipment and handling. The highest risk for temperature deviation (shipping excursion) is during the staging or handling of product at warehouse and airport locations. Most guidelines emphasize investigations after the temperature excursion occurs instead of focusing on a more proactive approach.

Common Causes of Temperature Excursions are:

1. Human error – failure to follow shipping container assembly instructions
2. Incorrect pre-conditioning of coolants
3. Incorrect pre-conditioning of product
4. Courier/carrier error
5. Excessive ambient heat or cold temperature
6. Shipping container not properly oriented - container on its side or upside down which alters thermal performance
7. Poor-quality construction or insulation material that is different from quality of material used for pre-qualification and alters thermal performance
8. For vehicle transport, the reefer temperature is beyond the pre-qualified shipper temperature range, moving product temperature beyond the limits
9. Faulty technical package design or manufacturing error

Pre-Qualified Shippers Only! – Why Isn't this Enough for Your Product?

Some companies reason that pre-qualified packaging can control product temperature within certain outside temperatures for a rated timeframe; therefore, it can be considered equivalent to temperature monitoring. The argument is that the temperature monitor is not necessary as long as the container does not exceed its pre-qualified duration (timeframe).

The risk from this argument lies with the incorrect assumption that the probability for excursions on pre-qualified shippers is extremely low. The vast majority of temperature excursions are due to human-error in which the pre-qualified shipper was assembled incorrectly and will not perform as designed. Most product temperature excursions could only be detected through the use of a temperature monitor.

Many users of pre-qualified shippers that do not contain a temperature monitor focus on duration of shipment rather than the temperature specifications of the product. These pre-qualified containers are accepted based on the vendor's Operational Qualification (OQ). In this case, a Performance Qualification (PQ) is not performed to evaluate if the shipping container can perform under the conditions that the product is normally shipped. This step may be damaging because the OQ is performed in a temperature chamber where the other stresses of the shipping activity are not present. In either case, the temperature monitor should be used to assess the shipping lane and evaluate operator performance.

Periodic versus Continual Monitoring

There is an instance in which the use of a pre-qualified shipping container alone is relatively low risk. A pre-qualified shipping container with reliable transportation across a specific route helps provide the shipper greater elements of control than more varied shipping methodologies. While this approach may increase control, variability still exists in the system, hence the need for periodic monitoring at the very least.

Periodic temperature monitoring will allow the shipper to confirm that the unique lane continues to perform as expected. The main point here is that the monitoring may be periodic rather than continual, assuming adequate data is updated and supports that activity.

Regardless, the temperature monitor still plays a critical role in documentation. Nicholas Buhay, Acting Director, CDER Division of Manufacturing and Product Quality, commented at the PDA conference in March 2006: "Documentation: ...Of course, we certainly adhere to the principle that documentation is a control in itself, and so therefore if the documentation is not done, the control has not been achieved. If the documentation is not done, the operation has not been performed."

The temperature monitor gives knowledge of where the shipping performance stands in terms of temperature control and it provides the required documentation.

Technology Features Available for Monitoring Temperature

Several types of temperature-monitoring devices in the market feature:

- Minimum and maximum temperature-reading thermometers
- Battery powered mechanical recording devices, or
- A variety of battery powered electronic devices that incorporate an assortment of operating features including:
 - pass/fail readouts
 - radio-frequency capabilities, such as RFID
 - computer connectivity such as USB, data storage, and local programmability

Temperature devices today provide many features including, identification of humidity, pressure, and visual, audible or electronic alarms. These can be single or multiple-use devices in a variety of sizes, features and cost.

Positive Aspects of Monitoring

- For high-value supplies, monitoring is a matter of not only detecting failure, but also assessing failure points that leads to improving the process.
- The courier can tell the time/location of the shipping container based on the data.
- Indicates when best to test record the ambient to see what effect the outside environment has on the shipping lane. (Note: Some pharmaceutical manufacturers commonly utilize internal and external monitors, particularly on more valuable shipments, so that the correlation between the two environments can be evaluated).
- Identifies and documents temperature excursion details - date, time and length.
- Provides graphs that show where temperature performance is positioned (within or outside the expected limits and trends).
- Triggers a need for training. An example is an early stage excursion that would trigger training on proper handling of the product or coolants.
- The data supports control of product through pipeline to destination.
- Decreases the possibility of human error because the staff takes a second look at the package, documents and assembly prior to starting the temperature monitor.
- In case of litigation, it helps determine alleged damages and responsibility by providing when, where and how long the temperature excursion occurred.

Lawsuits

In 2009, two lawsuits would not have had the evidence accepted if it were not for the use of the temperature monitor. The claim was that cold chain material was adulterated by the sued party. It was shown that the adulterated material could not be used due to exposure to excessive temperature. The data from the validated and calibrated temperature monitor documented the claim of excessive temperature exposure at the time the sued party had responsibility for handling the material. In the absence of temperature monitors and the data used in both lawsuits, the courts would not have recognized that damages occurred and been able to clearly identify the responsible party. Both lawsuits resulted in orders that the defendant pay for damages.

The temperature monitor reveals what previously could not be detected.

From a business standpoint, the benefit of using a temperature monitor is the assurance that it delivers information otherwise not available. The main elements in shipping are: logistics & freight (about 70% of cost), qualified or pre-qualified shipper (about 20% cost), and the temperature monitor (less than 10% cost). The lowest cost item in this list is the temperature monitor, yet the monitor is commonly left out to “save money.” This action lacks common sense because the lowest cost (investment) item can provide critical information (greatest return) about the performance of the logistics service provider and packaging, as well as whether the SOPs are being followed. Ultimately, the temperature monitor delivers proof of compliance and enables the evaluation of continuous process improvement.

Looking Forward

As pre-qualified shippers and temperature monitors are in common use, the next stage is innovation in rapid data interchange, expanded access to other delivery and data systems with greater functionality. The use of RFID is in limited use today. The introduction of the USB temperature monitor interface is one device that will return process benefits and productivity improvements many times beyond its initial costs.

Couriers will combine their database with temperature monitor database to identify who, what, when, why, how many/how much was at each stage of the shipment. This would deliver segmentation and computerize the total picture of the shipping activity across the supply chain. The signed or manual documents will be part of the electronic file readily accessible.

On a grander scale, the databases tie into larger networks that will integrate temperature data with logistics data to provide a more comprehensive tracking and analysis process. These systems would not only show product temperature of shipment on a specific date, but also show the ambient temperatures on the shipping lane, location of the shipment, and the delivery time. This would integrate with data from other networks to feed an intelligent, dynamic and adapting distribution network.

Further in the future, micro-sized temperature indicators will feature greater measuring accuracy with transferrable data and many other features tailored to the users' needs at a reasonable cost. A vision into the future would have the micro-sized part of the product secondary containers innovate to a nano-sized part of each primary container to assure each dose has a temperature history and is acceptable for use.

Conclusion

The trend of regulatory change is leaning towards strong guidance to use temperature monitoring for each and every shipment. The temperature monitor is the lowest cost component of the logistics process and it provides valuable decision-making information. If the data is harnessed properly, its many uses make it a valuable tool to assure compliance or address correction and improvements. Today, the affordable cost of monitoring, coupled with powerful technology, integrates information and positions continuous monitoring as a practical solution for temperature control.

Together, the reliable courier, qualified or pre-qualified shipping container, and the temperature monitor deliver a sound solution that has already succeeded in a rapidly growing temperature-sensitive shipping industry. Thanks to temperature monitoring, information is delivered to confirm, improve, and ensure that proper shipping conditions are maintained in the future.

Temperature monitoring provides the product with the least amount of risk. Any other way is just not worth the risk!

Glossary

Cold chain- refers to supply chain controlling materials that are temperature sensitive and must maintain a range. Generally, the temperature range referred to is 2°C to 8°C or 5°C± 3°C.

Controlled Room temperature (CRT) – describes temperature products that generally remain between 20°C to 25°C, with excursions allowed between 15°C to 30°C where mean kinetic temperature is less than or equal to 25°C. Definition is found in USP 29, General Notice section.

Design Qualification (DQ) – step in PDA shipping qualification process that provides documented verification that the proposed design is suitable to meet the requirements.

Operational Qualification (OQ) – step in PDA shipping qualification process that provides documentation that the design yields reproducible results when exposed to expected controlled conditions (typically performed in an environmental chamber). Refer to PDA Tech Report #39.

Performance Qualification (PQ) – step in PDA shipping qualification process that provides documentation that the design yields effective and reproducible results during actual shipments of the product or acceptable substitute. The shipping container that passes a PQ is “qualified for the product” for that specific type of route, duration and product load. A PQ must pass triplicate in testing. Refer to PDA Tech Report #39, 2007 revision.

Pre-Qualified shipping container (shipper) – This refers to a shipping container that has passed an OQ with broad temperature range and payload test in a laboratory. This broad range makes it pre-qualified for many conditions, however it may not be “qualified for the user’s product” over the user’s shipping route and handling conditions. That requires further testing.

Qualified shipping container – This container passes an OQ and PQ using the user’s product or equivalent substitute, the user’s unique shipping conditions and payloads. See PQ above.

Shipping excursion – same as product temperature deviation during shipment or excursion. These are events where the temperature limits of the product are exceeded during shipment. If the product label states that it is to be stored at 2°C to 8°C, then any event where the product temperature moves below 2°C or above 8°C would be considered a shipping excursion.

Shipping qualification – This term is used loosely to mean the shipping container has been tested using a number of approaches. The most formal approach is used by the PDA in Technical Report #39 using DQ, OQ, PQ and follow-thru monitoring. Refer to PDA Tech Report #39, rev. 2007.

Storage temperature conditions – these are the labeled temperature ranges within which investigational medicinal products (IMP in EU) clinical supplies in USA, and licensed drugs are to be maintained during storage, shipment and use. These are printed on labels on the primary or secondary packaging. Labeling and requirements for drugs are referenced in United States Pharmacopeia/National Formulary (USP/NF) and equivalent EU guidelines.

Temperature monitor – device that measures temperature and records the temperature readings over time. This generally covers the duration of the shipment. Usually includes alarm features to alert user that the temperature limits have been exceeded. Newer devices have many additional features including digital output and computer interface to

transfer data for graphic presentation.

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About Sensitech

As the world's leading provider of cold chain visibility solutions, Sensitech Inc. enables global leaders in the life sciences, industrial, and food markets to track and monitor assets across the supply chain in order to protect the integrity of temperature-sensitive products. Sensitech is an ISO 9001:2008 company based in Beverly, Mass., with over 30 sales, service and distribution locations around the world. Sensitech is a part of UTC Climate, Controls & Security Systems, a unit of United Technologies Corp., a leading provider to the aerospace and building systems industries worldwide.



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