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White Paper

Beyond the Cold Chain

Last mile transportation and subsequent user storage conditions present unique challenges when it comes to ensuring the safe and effective use of pharmaceutical products.

The author
Corneliu Tobescu, Chief Operation Officer

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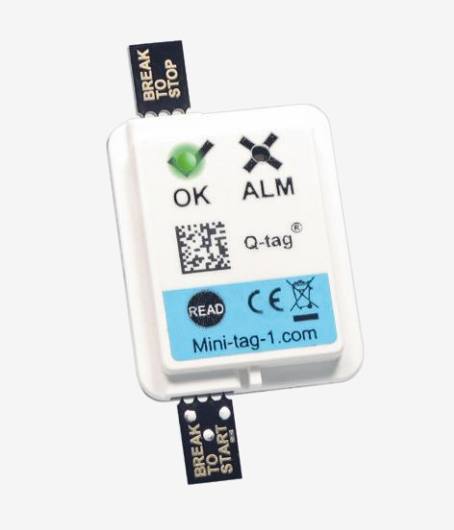

Introduction

Cold Chain logistics is a $10 billion component of the $1 trillion global pharma industry. Around 80% of drugs require temperature controlled transportation and the trend is distinctly upwards. In some drug categories the proportion is even higher. For example, according to the World Health Organisation, more than 90% of all vaccines require a temperature-controlled supply chain.[1]

The need for these controls is driven by the increasing sensitivity of modern drugs, particularly those of a 'large-molecule' i.e. biologic nature. It is a requirement that is underpinned by tight regulatory controls and compounded by factors such as globalised production, new market development and new systems of transportation. And the problem of maintaining the correct product temperature during shipment is not insignificant. According to industry sources the incidence of temperature excursions during pharma transportation may be as high as 5% of the total[2] and the World Health Organization reports that the Effective Vaccine Management assessment (carried out in more than 70 countries between 2010 and 2012) found that only 29% of countries met its minimum recommended standards for temperature control."[3]

Why we need electronic point-of-use temperature indicators

Electronic indication is necessary for drugs especially those that have poor stability characteristics and must be kept within narrow temperature ranges. Given the life- and health-critical applications for these drugs it is no surprise that electronic sensors are usually the preferred, if not only solution.

However electronic temperature monitoring, whilst bringing greater accuracy and other benefits to the table, can also have their downsides. Compared to chemical indicators they are expensive, they require a power source to operate and they can be of a physical size and weight that renders them inappropriate to many situations such as direct attachment to packaging.

Monitoring and maintaining the viability of medicines and vaccines is important for several reasons:

1. Product potency: the administration or ingestion of compromised products may have serious repercussions including mortality implications and the re-emergence or occurrence of preventable infectious diseases.

2. Waste and cost minimisation: Medicines and vaccines can be expensive and are often a scarce resource in remote communities with limited transportation infrastructure.

3. Confidence and trust: Programs to treat and prevent disease and illness, especially in developing regions, may be seriously undermined by the existence of ineffective or dangerous products.

Market Trends

Currently one of the biggest market trends in pharmaceuticals is the move towards biologic medicines and personalised, patient-centric remedies. The complex nature of biologics and vaccines means that they are often extremely reliant on the maintenance of a highly controlled environment in order to be fully effective or even be viable at all. With the basis for many of these treatments being living cells or complex chemical molecules there is significant risk of therapeutic loss or impairment in the event of unacceptable temperature exposures. In some cases such temperature deviation might not only result in a loss of potency, in some cases it could result in the product becoming dangerous due to the production of toxic degradation compounds.

It's not just the drugs themselves that are becoming more complex. The supply chains involved in moving these products around have become increasingly long, tortuous and diverse. Today's multi-step cold-chains require the effective seamless integration of a large number of parties across several shipping modes, climate zones, storage facilities and patient health facilities.

Difference between temperature loggers and time-temperature indicators

Freight temperature loggers or monitors are portable electronic devices that measure, record and, sometimes, transmit temperature data over a defined time period. This type of increasingly sophisticated and accurate monitoring is normally conducted during the primary shipment of pharma and bio-pharma products and is designed to ensure that the goods concerned are maintained within the prevailing GDP regulations and do not exceed the safety stability parameters that have been established for a particular product.

A time-temperature indicator is designed for a different purpose. Temperature indicators also measure temperature but rather than record data for subsequent analysis purposes, they monitor the accumulated temperature exposure over time and provide a clear, visual indication if a product has exceeded pre-determined temperature limits within this period. In this way they can be used to protect products from all the way from manufacturing to final use. These indicators can be either digital or chemical depending on the requirement.

And even when robust thermal management systems are in place and rigorously enforced, the problem is not necessarily solved. Simple human error or uncontrolled events are often the cause of unwanted temperature exposures. A vial left out of a fridge, an unexpected power dropout, random equipment malfunctions or incorrectly set temperature levels might spell the difference between life and death for an unfortunate patient further down the line.

Other circumstances where there can be life threatening breaks in the cold chain include the delivery of vaccines, clinical trial materials and other essential drugs into remote regions of the world where the infrasructure is often not available to ensure safe final-mile delivery.

Resolving this part of the equation may be one way of relaxing the regulatory leash when it comes to temperature management but it is not a guarantee that a pharma product is going to be safe and effective at the point of consumption or administration. This is because once the product leaves the controlled-temperature supply chain environment it often enters a ‘no-man’s land’ where little might be known about the correct handling and storage of sensitive drugs and even less might be known about the consequences of taking thermally-compromised medicines.

Vaccines are particularly susceptible to temperature extremes

Medicines in the home are rarely temperature managed

The Regulatory Position

It is important to realise that regulatory authorities require that a manufacturer ensures product quality not only during storage and transport but until the drug concerned is used for patient treatment. For example the International Conference on Harmonisation stipulates that that "The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use."[4]

This stipulation presents a formidable hurdle for a pharma manufacturer, since the conditions for product safety must be safeguarded even after the controls by the manufacturer in the primary supply chain have come to an end. This, for example, would include the transfer and storage of pharmaceutical products to and from pharmacists, retailers, hospitals and community doctors and even extends to when consumers take and store the product at home.

Official guidance in this respect is unequivocal and invariably recommends that drugs that are subjectively judged at point of use to be degraded or out of tolerance should be discarded. For example, the Centers for Disease Control and Prevention in the US says that it is dangerous to administer vaccines where the temperature history is unknown or uncertain. "It is better to not vaccinate than to administer a dose of vaccine that has been mishandled."[5]

Bedrooms are a favourite place for storing medicines

Domestic Safety

How many bathroom cabinets and kitchen cupboards are full of pharma products that are of questionable quality?

Today's consumers are much too busy to read the fine print of every pharma label that comes their way. Few are competent to judge whether a product they buy or have stored for a time is safe or fit for purpose. Practically none can vouch for the temperature storage record of their household pharma supplies.

A recent study[6] provided the users of a temperature-sensitive biologic drug with a data recorder to monitor the real storage temperature conditions that were being used. The results were startling. Out of 255 participants in the study only 17 (6.7%) had stored their medication within the recommended temperature range. Of those who did not, 24.3% had stored their medication for more than 2 hours outside of the recommended range.

The author of this report did not evaluate the effect of these storage conditions on the biologic activity of the medication but speculated that storing these medications outside of the recommended temperature range may adversely affect their efficacy. The paper posed the following scenario: "What if, for example, a tumor necrosis factor antagonist is just the right biologic agent for a patient's disease, but the way the patient stores the drug leads to drug breakdown and suboptimal efficacy? Rheumatologists may not even be aware of this and change medications, when all that was needed was better instruction on storage."

Last-mile logistics and the storage of medicines at home present particular problems in remote and developing communities

The stock-piling of prescription and OTC drugs is prevalent in many countries

Remote Controls

Final mile delivery and household storage has different connotations when we start to talk about the situation in underdeveloped nations.

There is a huge potential for life-threatening breaks in the cold chain when we consider the delivery of vaccines, clinical trial materials and other essential drugs into remote regions of the world. In these situations the infrastructure and qualified staffing are often not available to ensure safe final-mile delivery nor the necessary intervention systems to allow impaired products to be removed from the supply chain.[7]

In many countries, due to general drug scarcity, high prices and a lack of community medical services, there is a long-standing tradition of stockpiling drugs in the home for 'emergency' use. This often results in seriously out-of-date medicines being kept in wholly inadequate storage conditions. One study in Sudan, for example, found that 97.7% of households were storing medicines.[8] Apart from drugs that are being used or on-going treatment such medicines are usually treatment leftovers or obtained from OTC sources when available and accumulated for future use. The climatic extremes in many of these countries compounds the risk of deterioration and expiry.

In a survey of in-home drug storage in Iraq conducted in 2009 it was found that a majority of households (94%) stored drugs at home with only 31% of these being used for current medication purposes. Nearly 60% of the drugs were deemed to be kept in inappropriate storage conditions, a figure that is of particular concern in a location where the summer heat can reach up to 50°C.[9] Another study conducted in Saudi

The storage conditions of household medicines by consumers is often poor or inappropriate

Arabia found a mean of eight drugs stored per household, and up to 30% had at least 10 medications in their home.[10] A similar situation was found to exist in Qatar where poor levels of patient-pharmacy interaction were cited as a reason low awareness of correct storage practice.[11]

These findings indicate a pressing need to extend temperature management in the direction of the final consumer. A reliable point-of-use temperature indicator is a means of ensuring that drugs that are consumed or administered at home or away from direct medical supervision are not outside acceptable margins for safety in terms of temperature history.

By the same token, there will be many drugs that are discarded because little or nothing is known of their temperature record even though they are fit for use. The presence of an accurate temperature indicator means that drugs can be consumed during their 'safe period' reducing unnecessary drug wastage and minimising the consumption of potentially dangerous drugs.

Many vaccines and biologics are especially sensitive to cold environmental conditions

The Challenge Of Low Temperatures

The problem of temperature control is not confined to high temperatures. Medicines, especially vaccines, can be very sensitive to cold conditions and, according to the World Health Organisation, "protecting vaccines from freeze damage remains one of the most poorly addressed problems in vaccine management."[1]

Typically, shipping and storage guidelines advise that vaccines and biologics must remain between 2° and 8° Celsius, the temperature span that is the basis for much of the data on which stability parameters have historically been derived.

"Vaccines are highly thermo-sensitive biological substances which have a fixed shelf-life and lose viability over time. The loss of viability is irreversible and accelerated if proper storage and temperature conditions are not maintained. A vaccine vial must remain between 2 and 8 degrees Celsius throughout the entire cold chain system - when it is transported, when it is stored in a refrigerator or cold store, and when it is used at an immunization session."[3]

Although many sensitive drugs fall into the nominal 2-8 degrees temperature band others require very specific storage conditions and these conditions must be maintained until the point of administration. The HPV vaccine[12], for example, can withstand higher temperatures but is extremely sensitive to freezing and cold conditions.[13]

One systematic literature review that was carried out[14] concluded that "accidental freezing is pervasive and occurs across all segments of the cold chain. Between 14% and 35% of refrigerators or transport shipments were found to have exposed vaccine to freezing temperatures, while in studies that examined all segments of distribution, between 75% and 100% of the vaccine shipments were exposed."

Electronic v Chemical Indicators

Chemical-based indicators are of value in certain situations. They are cheap, do not require a power source and are very low bulk. However they are associated with a number of limitations which disqualifies them for some medical applications.

These limitations include:

ACCURACY:
The accuracy level for a chemical indicator may be in the order of +/- 2 degrees C.

SPEED:
Chemical indicators can present potential problems with speed of reaction which might be too slow to react to destructive temperatures.

READABILITY:
The readability of a chemical result or colour change can be subject to interpretation in different ambient lighting conditions and by the different colour-vision capabilities of individuals.

INTERPRETATION:
Some chemical indicators my require interpretational skills that are not inherent in a typical user.

VALIDATION:
It is not possible to be pre- or post-operationally validate chemical indicators to ensure accuracy of measurement.

CUSTOMISATION:
With chemical indicators no threshold settings or customisation is possible.

COMPLIANCE:
Chemical indicators may be inadmissible in terms of compliance with regulatory thermal monitoring requirements.

STORAGE:
Chemical indicators can present storage/ transport limitations or problems due to deterioration of chemical ingredients.

PRE-CONDITIONING:
Chemical indicators may require preconditioning before use.

SAFETY:
The chemicals used in some indicators may themselves be toxic or they may have the potential to contaminate adjacent medicines.

TEMPERATURE RANGE PERFORMANCE:
Most chemical indicators are unable to measure exposure to freezing temperatures. This can necessitate the use of two indicating devices, adding to the cost and complexity.

Summary

How many drugs are thrown away due to being judged unfit for human consumption at point of use? How many drugs are consumed that are outside the official margins for safety? These are serious issues that to a large degree can be addressed through equipping individual medicine containers with inexpensive temperature indicators that are accurate, reliable and easy-to-use. Such a safety feature will reduce waste and, improve curative outcomes. It will also grant the drug supplier with a huge market differentiator and positive brand reinforcement.

Furthermore, the incorporation of an electronic temperature indicator will provide an additional barrier to counterfeiting and consumer confidence in the drug will be dramatically increased if users can see for themselves whether a product is fit for consumption.

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The Mini-Tag Indicator from Berlinger

Small but extremely powerful. With its LED indicator, which displays green for OK and red for ALARM, the Berlinger Mini-tag® enables you to respond quickly, easily and confidently to changes in temperature. Up to three different alarm limits can be set for temperatures between -25 °C and +55 °C. The measurement interval for the temperature can be set between 1, 5 or 10 minutes, depending on your requirements. With an operating life of up to three years, the Berlinger Mini-tag® is the perfect companion for “Last Mile” monitoring on primary and/or secondary packagings.

Talk to Berlinger

Berlinger are interested in working in partnership with shippers and logistics companies that have need for controlling the cold-chain beyond the point of bulk delivery. It would also welcome discussions with active and passive packaging suppliers that are offering final mile and direct to patient logistics solutions.

The Mini-tag from Berlinger is a tiny electronic indicating device designed for direct attachment to containers, packagingor delivery devices

A unobtrusive Berlinger Mini-tag® seen attached to pharmaceutical primary packaging

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Berlinger & Co. AG Switzerland +41 71 982 88 11
Berlinger USA LLC +1 508 366 0084
info@berlinger.com | www.berlinger.com