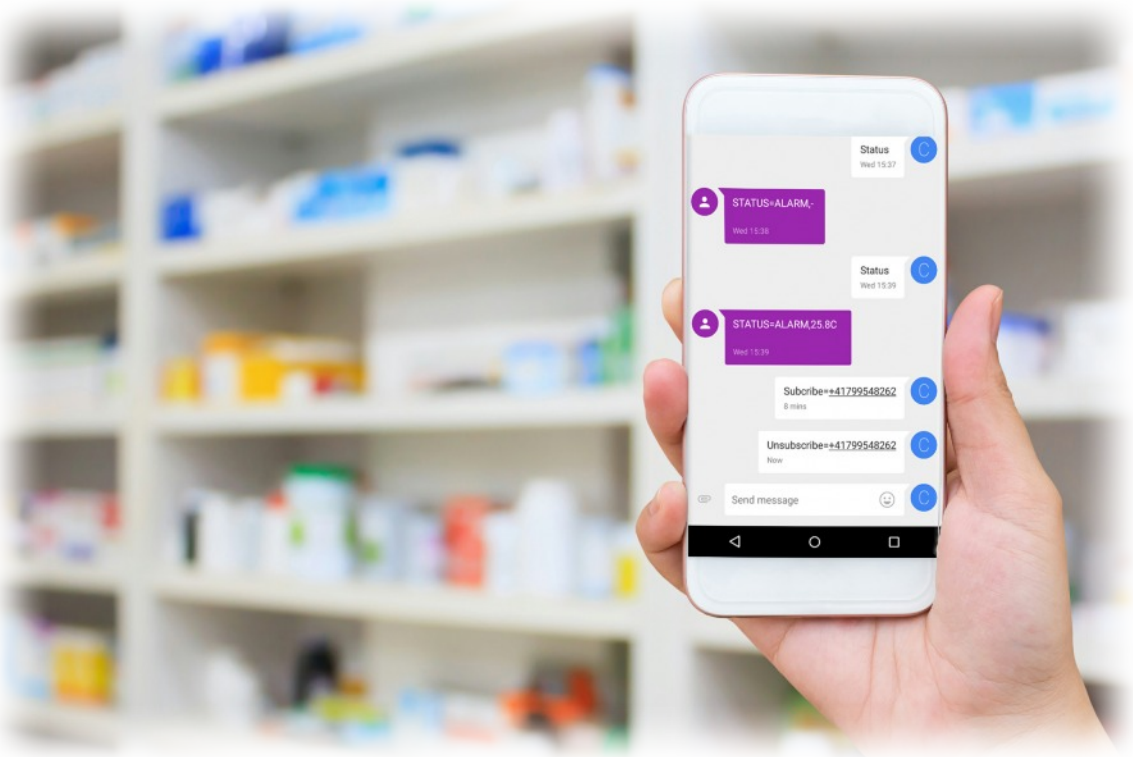
White Paper

# Towards real-time temperature monitoring

Wireless data-logging systems for the continuous collection of temperature information during pharmaceutical transport and storage.

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> *Temperature excursions during transport are not rare events. According to information obtained from many sources and during international conferences, excursions happen at a frequency of 1% - 5% of transport events. This places transport as one of the least reliable pharmaceutical processes.(28)*

### Introduction

In June 2017 global news reports contained the alarming news that a 'vaccination error' involving 300 people in South Sudan had resulted in the deaths of at least 15 children and the severe illness of 32 others.(1) The vaccine concerned was an immunisation against highly contagious measles virus and it turned out that the batch of vaccines concerned had been exposed to unacceptably high temperatures.

Although it is not often that stories like this hit the mainstream press, such incidents are not isolated events. In March 2017, thirty-seven people were arrested in eastern China over the selling of illegal vaccines that had not been properly refrigerated or transported.(2)

The fact is that pharmaceutical drugs are complex chemical or biological preparations that can be rendered ineffectual, or even toxic, if they are subject to extremes of temperature. Temperatures that are too high promote pathogenic growth while freezing reduces the efficacy of medicaments containing proteins. This temperature sensitivity has resulted in a requirement for temperature traceability by means of a measured temperature history to become a mandatory element of GDP compliance.

Few, if any, pharmaceutical products are unaffected by extremes of temperature. Even the simplest medicines are comprised of chemical constituents which exhibit varying degrees of lability when exposed to heat or cold. Some medicines however are particularly quickly and dangerously affected by temperature variations. They might become totally inactive or lose their therapeutic potency which can be a life-threatening result or, in the case of vaccines, leave the recipient unwittingly exposed to dangerous pathogens.

The effects of temperature on biological drugs and vaccines is well documented and these 'living' medicines are easily damaged. One study, for example, showed that insulin stored for 28 days at an ambient temperature of above 30°C showed a decrease in potency and biological activity of up to 18% compared to the same product correctly stored at 5°C.(3) Furthermore, in many cases, the effects of temperature degradation is cumulative.(4) And each exposure to a temperature elevation results in a progressive and irreversible degradation of potency.

It is not only hot temperatures that are a threat. Most vaccines and some drugs like insulin will lose their effectiveness if they freeze. The problem is that with most medicines it is impossible to tell visually if they have been exposed to damaging extremes of temperature. Most will look no different after a deleterious exposure.

### 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. 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.

### What is a Temperature Excursion?

“A temperature excursion is the deviation from the labelled storage condition of a product for any duration whether during transportation or distribution. Studies indicate that if there is exposure of product or intermediate beyond specified environmental limits for substantial time, there shall be generation of impurities as a result of product degradation. Such degradation products are not only regarded as undesired but also shall have adverse reaction to the patient’s health.” (10)

# Conventional temperature logging

Although there is a widespread understanding of the need for controlling the temperature of drugs during storage and transportation, much of the monitoring that takes place still follows outdated practices that involve intermittent physical readings, manual data entry and old-fashioned reporting and sharing methods. This introduces delays and inconsistencies that can greatly undermine the entire temperature surveillance process.

## Evolution of temperature management

In the earliest days of pharma temperature monitoring, the product temperatures were simply measured using standard mercury or alcohol thermometers. This system was limited to the periodic manual inspection and recording of single-point temperature measurements. Although fragile ‘max-min’ thermometers could indicate the lowest and highest temperatures reached they were not time able to pinpoint the time of occurrence. Over time, at least for some applications, this manual thermometer analysis gave way to visual chemical temperature indicators.

These are heat-sensitive labels register a visible change in colour when subjected to a pre-determined temperature limit. Like thermometers, these ‘accept/reject’ alerts are point-in-time indicators which require subjective visual appraisal. Nonetheless, although they have limited accuracy, limited shelf life and need training in use, these indicators are very cheap to produce and are not easily damaged. It is these benefits that have ensured that chemical indicators remain in widespread use, especially in the distribution of vaccines in developing regions. However, their limitations in use are seeing them being gradually replaced by more reliable, more accurate and more functional electronic temperature tags.

A big breakthrough in temperature management came when time- and temperature-sensitive data loggers started to be widely used in the 1970s and 1980s. These are battery-powered temperature recorders capable of virtually continuous temperature measurement which can store the data collected on-board until it is possible to extract it to an external device or system for subsequent interpretation, analysis and distribution. However although this new functionality made reliable temperature monitoring much easier, a reliable temperature management regime was still heavily dependent on manpower resources, time, training and special equipment. The cost and effort involved can result in both the frequency and extent of temperature checking being compromised and is one of the reasons why organisations such as WHO strongly recommend that, wherever possible, the process of recording temperature data should be made automatic.(6)

## New age devices

There is no doubt that these semi-automatic time-and-temperature devices represented a step-change in temperature control, with these devices a shipper still has to wait until it receives a shipment and downloads the data from the temperature logger before it finds out if a drug’s temperature has been compromised. However, the latest generation of data-loggers which come with integral data transmitters are taking temperature monitoring to another level. According to an article in World Pharmaceutical Frontiers: (7) "up to just a few years ago, the radio transmitters in these devices were only powerful enough to be short range, today, mobile-phone radios can be incorporated into them, allowing each recorder to communicate directly with the cellular network. Not only does this give operators flexibility when it comes to choosing vendors but it also means the infrastructure around temperature monitoring is a lot less costly to develop."

### Why it is important to keep up-to-date

It is increasingly necessary to have the ability to capture and share data quickly. If a system is not kept up-to-date then either the temperature monitoring will not be carried out effectively or operational staff will be forced or encouraged to adopt informal, non-compliant methods in order to carry out their duties effectively.

An example of this in the health sector came in the form of a recent report(5) by the BBC which showed that UK healthcare professionals are widely using unauthorised social media platforms such as Snapchat and WhatsApp in order to quickly share potentially sensitive clinical data amongst fellow medics.

According to this news item UK medical staff are only authorised to share and distribute such data via facsimile machines and basic alphanumeric pagers. This out-of-date technology severely hampers the ability of medical staff to communicate and as much as one third of UK doctors may be using unofficial, and illegal, messaging apps for the sharing of patient information.


## On demand, shared-access monitoring

The combination of new-generation devices and the latest data transmission, capture, sharing and analysis technologies that can be implemented on the digital cloud is the latest development in pharma temperature monitoring.

The cloud is revolutionising data collection and dissemination while advanced data analytics is helping to interpret the huge volumes of data that is collected. Continuous and virtually continuous temperature measurement with both local and remote storage is opening the door to predictive temperature analysis with the emphasis on the dynamic control of storage spaces rather than post-event reactive responses. The problem with most digital temperature loggers is that they must be connected to a host device in order to download recorded data which means that, in practice, they have no real-time data interactivity. The result is after-the-fact analysis for claims, loss in quality and related issues.

As one cold-chain practitioner put it: “some in-built systems are reactive or historical in nature rather than preventative or predictive. In other words they effectively tell you that a product's safety envelope has been violated, rather than tell you that it is in danger of being violated. The way things are at present, there can be lengthy gaps, not in the recording of information, but in its timely receipt. Knowing that something has been corrupted or contaminated after it has happened is of great benefit in preventing the affected product entering the chain of consumption, but it has no preventative value other than the learnings that might emerge from a post-event inquest”.(8)

In contrast, with a real-time monitoring system, the data-logger will alert the shipper in advance to temperature conditions that might result in product impairment or regulatory non-compliance. The focus in the first place therefore becomes one of predicting and eliminating cold-chain breaks and temperature excursion incidents rather than on detecting and removing violated products from the supply chain. It is a change in emphasis that means that the big challenge ahead will be less about capturing the data and more about the ability of supply chain stakeholders to successfully analyse and act timely on the complex data that is generated.

## Some drivers for continuous temperature monitoring

There are several factors that are stimulating the demand for improved temperature integrity:

- Introduction of new direct-to-patient strategies
- Growth in sensitive biotech and biogeneric products
- Increased regulatory oversight of pharma including CRT products
- Adoption of risk-based logistics strategies
- Technological developments including cloud storage and wireless communications
- New supply chain integration models for improved data transparency and sharing
- Continuing investment in coldchain infrastructure around the world
- Temperature monitoring data has been successfully used to pursue claims for third-party product damage (12)

# Benefits of real-time monitoring

There are several benefits from investing in the latest temperature-monitoring equipment including the possibility of reacting quickly to a temperature event and the ability to make better decisions based on continuous live data.

When an alarm event occurs, the difference between instant notification and a post-event notification several days, or even weeks, later might be the difference between a safe shipment delivery or millions of dollars of product write-off, a regulatory investigation, mountains of bureaucratic hassle and, most important of all, potentially failed patients.

- **Automatic alerts**

  Real-time temperature monitors with GPS capabilities can trigger automatic alerts when fixed temperature limits have been exceeded or when predetermined temperature patterns have been recorded. The immediacy of the notifications means that it can be possible to prevent, mitigate or rectify the consequences of a temperature excursion and prevent costly product damage. For example, if it was known that a pharma product had been exposed to potentially damaging temperatures during a sea-freight leg, a back-up shipment could be dispatched by air even before the affected reefer arrives.

- **24-7 data access**

  A cloud-based monitoring platform fed by wireless dataloggers permits immediate access to temperature data from practically anywhere in the word for immediate action.

- **Multiple, simultaneous data sharing**

  Different supply chain stakeholders can be afforded controlled access to temperature information as it happens which means that potential problems that may arise during shipment can be addressed in advance.

- **Cost-effectiveness**

  As well as minimising the need for local scrutiny, exception reporting allows numerous devices to be accessed and monitored from a single location for a very cost-efficient service.

- **Proof of Regulatory Compliance**

  The concern of regulatory bodies is to provide consumers and patients with products that are safe and have full therapeutic properties. “Regardless of the mode of transport, it should be possible to demonstrate that the medicines have not been exposed to conditions that may compromise their quality and integrity.”(9)

  In order to demonstrate regulatory compliance therefore requires documentary proof of temperature management and this recorded verification is a mandatory element of all GDP regulations and guidelines. And in cases where a GDP auditor might require sight of temperature records, the ease of sharing and ready availability of digital temperature data is a huge benefit. If these records are scattered throughout the supply chain and stored in different formats it might be very difficult to demonstrate compliance.

### The risks of neglecting temperature effects

"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." (12)

## Need for continuous monitoring

Shippers need to know the where, when and why of temperature fluctuations since a vast proportion of temperature excursions might go completely unnoticed if a temperature monitoring device is not utilised.

Even where a pharma products or preparation is transported in a pre-qualified, purpose-built, active or passive container, there can be many reasons why the shipping container does not perform properly.

Typical causes of temperature excursions are:

- Unanticipated ambient temperatures exceed design limits of container/cover
- Unforeseen delays in transportation - e.g. airport apron delays resulting in solar exposures
- Human error - e.g. failure to follow shipping container assembly instructions; failure to hook up to refrigeration power source.
- Failure to use correct cold-chain solution e.g. qualified refrigerated reefer
- Exposures to 'greenhouse effects' of solar gain especially where pallets are wrapped in clear plastic film
- Weak links in the cold-chain and multiple hand-offs
- Climatic extremes - hot and cold ambient conditions, varying with time and season
- Lack of power connections for active units
- Unreliable power supplies for active units
- Lack of cold chain infrastructure - cold storage, dry-ice availability; local refrigerated transportation etc.
- Inadequate training and controls for logistics and medical personnel; lack of GDP awareness
- Incorrect assembly of collapsible containers
- Imprecise pre-conditioning of shippers and phase-change coolants
- Inadequate pre-conditioning of product
- Poor container or reefer packout

It has been observed (10) that even where correct storage conditions are maintained at the manufacturing site, these conditions are often not maintained meticulously during subsequent transportation (see Fig 1.)

Many studies have illustrated the huge variability in temperatures that can take place over time during storage and transportation even with validated cooling equipment and facilities. One study(11) in the perishables sector, for example, using countrywide data from across Greece, showed that "significant temperature fluctuations" and sharp temperature increases of as much as 12°C were exhibited during transportation between production and retail outlet (see Fig 2).

## Some definitions

**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"

**Controlled Room Temperature (CRT) products** refers to products that are generally required to be stored and transported main at temperatures 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.(22)

**Good Distribution Practice (GDP)** GDP requires that medicines are obtained from the licensed supply chain and are consistently stored, transported and handled under suitable conditions, as required by the MA or product specification.(23)

**Mean Kinetic Temperature (MKT)** Mean kinetic temperature is a simplified way of expressing the overall effect of temperature fluctuations during storage or transit of perishable goods. According to the US Pharmacopeia the MKT "is defined as the single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures."(22)

**Stability** The term stability, with respect to a drug dosage form, refers to the chemical and physical integrity of the dosage unit and, when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination (22)

**'Real-time' Temperature Monitoring** when an event or function is processed instantaneously it is said to occur in 'real-time'. To say something takes place in real-time is the same as saying it is happening 'live' or 'on-the-fly' (23). The term 'near real-time' usually refers to real-time + computer processing time + data transmission time. These additional time values are usually in the order of seconds or micro-seconds and for the purposes of temperature monitoring the two terms can be deemed as equivalent.

**Temperature Mapping** A mapping study establishes the temperature distribution within the zone being mapped and it locates hot and cold spots. The collected data provides an essential source of information to ensure that all Time and temperature-sensitive Pharmaceutical Products (ttspps) are correctly stored within their labelled temperature range(s) (25)

**Qualification** The action of proving that any premises, equipment and supporting systems work correctly and actually lead to the expected results. The meaning of the word validation is sometimes extended to incorporate the concept of qualification. (25)

**Validation** Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting pre-determined acceptance criteria. (27)

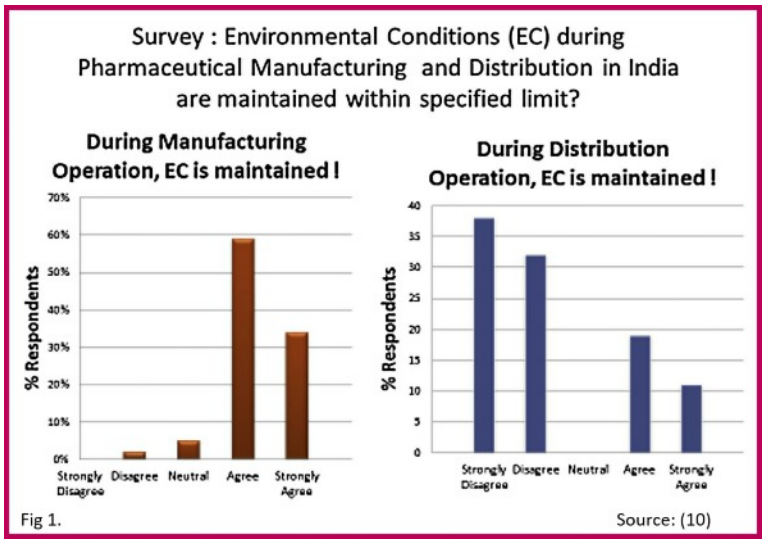


Fig 1. Source: (10)

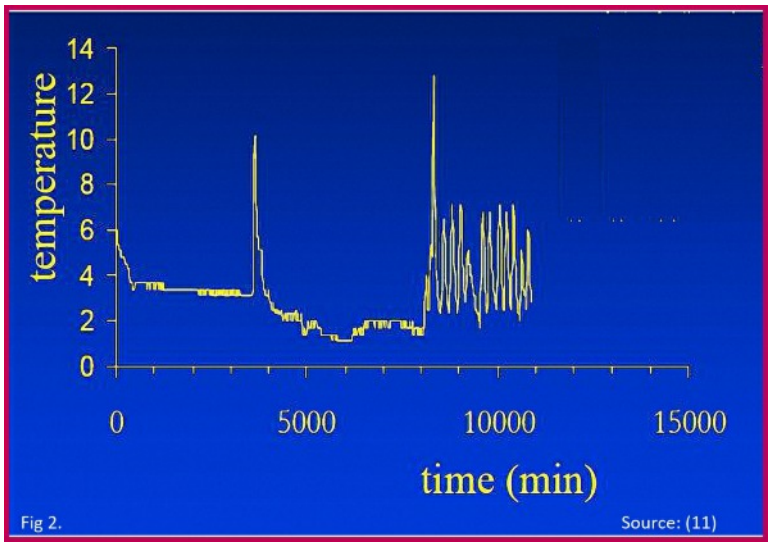


Fig 2. Source: (11)

# Do we really need to monitor pharmaceuticals?

There can be huge variations in the environmental, handling and equipment conditions encountered even on a single shipping lane. Although continuous temperature monitoring is not necessarily a compulsory condition of Good Distribution Practice, should a shipper decide not to implement constant monitoring then it is required to conduct a rigorous risk assessment at the planing stage of each route in order to justify the absence of constant monitoring (13). If a satisfactory risk assessment is not undertaken or if such an assessment demonstrates that continuous monitoring is necessary then an appropriately qualified temperature recording system must be put in place.

With so many recognised risk-points in the cold-chain, with the implications of minor packaging damage (a common occurrence in pharma-logistics) being unknown and with most 'prequalified' packaging being qualified in static chambers rather than in operational shipping lanes, there are few situations where it would be appropriate or acceptable to eliminate periodic or continuous temperature monitoring (See Fig 3).

As cold-chain specialist Sue Lee puts it: “Evolution in cold chain packaging is almost meaningless without tools to ensure a shipment’s integrity. Research shows that most temperature excursions occur within a mile of a shipment’s destination — meaning we need technology capable of monitoring a temperature-controlled shipment from packing through transport, storage and delivery”.(14)

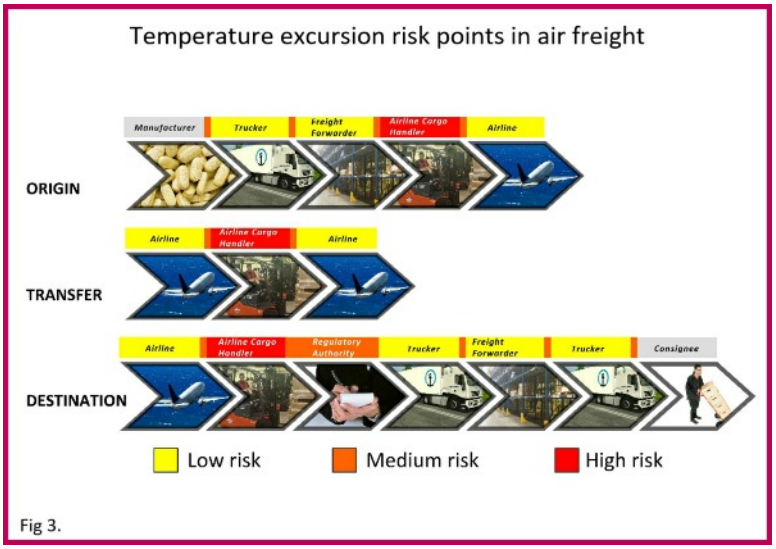


Fig 3.

## Justifying the cost

Millions of dollars of medicines and vaccines are unnecessarily discarded every year due to concerns about storage conditions or expiration dates. In fact, an estimated $10bn worth of pharma products are condemned each year(15). How much of this is down to product degradation during storage and transportation is not known but it is likely to be a sizeable figure.

However, the real cost of cutting corners on temperature management relates to the potential for lost lives or poor therapeutic outcomes as a result of compromised medicines. Without continuous monitoring, the length of time a product has been out of range is unknown necessitating the product to be withdrawn. Technological advances and economies of scale have made continuous temperature monitoring an affordable and reliable process and since it is possible to see both the duration and extent of an out-of-range temperature violation it is possible to determine if a product remains safe to use based on its known stability characteristics.

## Challenging environments

Some particular circumstances present particular challenges for temperature management:

### Clinical trials

Clinical trials present particular challenges for temperature monitoring. "Ensuring drugs are stored at the right temperature during transit is crucial throughout the entire pharmaceutical supply chain; an excursion from the prescribed temperature range can compromise product efficacy and, therefore, patient safety. But nowhere is this more important than during the clinical supply process – to ensure the safety of trial participants, and guarantee consistency of results between and within batches of drugs."(7)

Importantly, in the case of clinical trials, there is unlikely to be any reliable stability data in existence and the need for very tight temperature monitoring becomes even more critical. A simple failure to ensure temperature integrity might invalidate an entire test program and could be enormously wasteful in terms of cost and time. In particular, an unnoticed or unrecorded temperature excursion may result in the clinical results of the trial being compromised with all the attendant implications in terms of safety and cost.

## Emerging markets

Poor communications, lack of trained personnel, regulatory differences, political risks and lack of education can lead to difficulties in maintaining an effective cold chain in many underdeveloped countries. But, perhaps of even greater significance is a lack of cold chain infrastructure: “The cold chain faces many challenges - temperature integrity, data monitoring, storage and regulation among them - and where infrastructure is less established, these become harder to overcome.”(16) It's a challenge that is regularly faced by PATH, a nonprofit leader in global health innovation that has been advancing healthcare in disadvantaged nations for over 40 years. “Keeping temperature-sensitive health products properly cooled in extreme climates, over barely accessible roads, and in places with unreliable access to electricity is a constant challenge for developing-country health systems".(17)

## Vaccines

Vaccines are biological preparations that can be particularly temperature-sensitive and many lose their therapeutic efficacy when exposed to temperature extremes. The World Health Organization has reported that in a vaccine management study carried out in more than 70 countries between 2010 and 2012, as few as 29% of countries met its minimum recommended standards for temperature control.

One systematic literature review that was carried out(18) 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.”

PATH reports some of the consequences of these failures: "Strong cold chains are vital for immunization programs. They can also be extremely challenging to maintain, especially in low-resource settings with unreliable electricity, poorly maintained equipment, and long distances between facilities. As a result, health workers are sometimes forced to discard vaccines that they suspect have been exposed to extreme temperatures. Worse, they may inadvertently administer damaged vaccines, leaving people vulnerable to disease”.(19) According to Village Reach, a Seattle-based partner oranisation of PATH, a big part of the solution rests in “investing, testing, and introducing new cost-effective technologies that provide continuous temperature monitoring and recording“.(20)

## Last mile Delivery

Real end-to-end, temperature monitoring right down to point of use remains an elusive goal in many especially emerging markets and after an OTC or self-administered pharma product gets into the hands of a final consumer. For more details see Berlinger white paper “Beyond the Cold Chain” (21)

## Assessing the risks

Due to the high safety standards required, transporting pharmaceutical products is always an exercise in risk management. Since the physical movement of pharma products has the potential to affect the efficacy and quality of a product it is is important that adequate controls are in place to control risk. For example, transportation validation and temperature mapping are both essential ingredients of an overall pharmaceutical quality control process. This is because it is essential that a systematic approach is in place for collecting and analysing the necessary data to give 'reasonable assurance' and 'documented evidence' that a specified storage and coldchain system and protocol will consistently operate as within specified parameters.

### Temperature mapping

Storage areas have micro-climates as a result of convection currents, volume, shape and positioning of stock, type of storage racking/shelving, windows and access points, size, height, shape and orientation of room, airtightness of building, type of lighting etc. To store pharma products safely therefore necessitates a thorough monitoring and analysis of all the differences and changes in temperature that occur within cool rooms, fridges, freezers and warehouses due to localised influences. It is important that this analysis is conducted under different stock-holding conditions e.g. unit empty, unit part filled, unit full.

The World Health Organisation, for example, recommends that organisations storing vaccines should not accept a new cold room or freezer room from an installer until it has been fully mapped as part of the commissioning procedure and qualified. Vaccines should not be stored in the room until the temperature mapping exercise has been completed and the results have been analysed to identify and address performance gaps.

> ***"The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light.***
>
> ***This information helps us to establish a re-test period for the drug substance (API) ir a shelf-life for the final products and recommended storage conditions." (30)***

### Temperature bands

All temperature-sensitive pharma medications have different chemical compositions and this means they are all potentially affected in different ways by the application or removal of heat. In practice this variability has largely been overcome from a transportation and storage perspective through the use of standard 'temperature ranges' to which products with different prescribed temperatures limits can be assigned. These temperature bands, and any allowable temperature excursions from them, are generally derived from stability data from product tests.

Typical temperature bands are 2 - 8°C and 15-25°C but it should, be noted that the main regulatory authorities do not refer directly to these bands in their guidance documentation. Good Distribution Practice (GDP) Regulations from the EU, for example, simply state that products must adhere to the temperature restriction on the outer packaging or as otherwise described by the manufacturer.

### Product stability

Unless the pharmaceutical manufacturer stipulates otherwise, the temperature limitations of a pharmaceutical product are dictated by the mandatory parameters shown on the product's primary or secondary packaging labelling.

Limited excursions from the specified temperature bands can be tolerated in certain occasions where reliable stability data exists properly supported by documented temperature data. Some parties, however, are not happy with this relaxation provision, claiming that it opens the door to potentially dangerous 'rule-bending' and uncertainty.

Stability data is only of value if the degree and duration of a temperature excursion incident is known. Being armed with accurate temperature data that has been collected on a continuous basis allows quality personnel to quickly ascertain whether a shipment that has been subject to temperature excursion is either safe and useable, or unsafe and adulterated.

In this respect pharma products in transit should be considered little different from pharma products in a static cold-store environment. Of course to maintain cold- and cool-chain temperatures during transportation adds a number of additional difficulties but both expert opinion and common-sense suggest that it is much safer to rely on a combination of rigorous temperature monitoring and qualified packaging than to fall back on stability data that may have been generated under test conditions that do not fully reflect the real operating environment.

**Drug Product Stability**

**Testing Frequency & Storage Conditions**

| General case Study | Storage condition | Testing Frequency | Minimum time period covered by data at submission |
|---|---|---|---|
| Long term* | 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH | 0, 3 ,6 ,9 , 12 mo. 18, 24 mo. 36 mo., and annually | 12 months |
| Intermediate** | 30°C ± 2°C/65% RH ± 5% RH | 0, 6 ,9 , 12 mo. | 6 months |
| Accelerated | 40°C ± 2°C/75% RH ± 5% RH | 0, 3 , 6 mo. | 6 months |

* It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

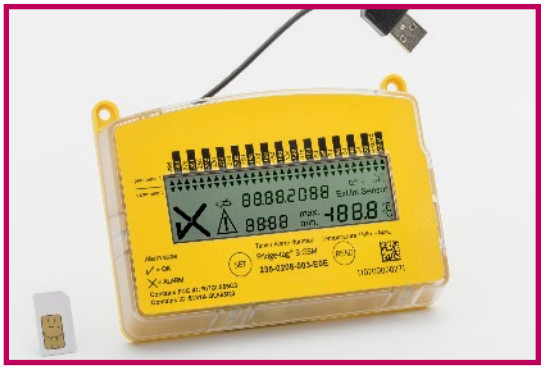
** As a result of "significant change" at the accelerated storage condition. If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

Fig. 3 Source: (29)

## The transmission of data during flight

Safety considerations and conflicting regulations in the US and Europe governing the use of 'transmitting portable electronic devices' (T-PED) means that, while approved dataloggers are permitted to continuously record in-flight temperature data, this data cannot be transmitted onwards during flight. Instead, the datalogger must switch off (usually automatically) on take-off and resume transmission on landing. This means that during the flight there is an effective blind-spot in terms of data transmission. And even if standard GPRS transmission was permitted it would not necessarily make a huge difference since there are huge tracts of land and ocean which do not have a terrestrial cellular infrastructure.

Instead, work is progressing on new solutions and approvals which will permit in-flight low-strength GPRS signals to be bundled together and transmitted using a flight-safe radio frequency. The use of picocell technology is one such development and this is already used extensively with some non-US airlines such as Emirates and Virgin Atlantic to allow passengers to make in-flight telephone calls using their standard mobile handsets. Note that sea, road and rail freight do not have the same safety issues and are not affected by the flight restrictions. In some cases, however, there may be issues relating to signal obstructions from container materials.(26)




## Summary

The future of pharmaceutical temperature monitoring is real-time. The ability to get instant notifications/alerts when a specified data value goes out of range and potentially before a pharma product enters the thermal danger-zone is an exciting proposition.

With the potential to allow administrators to review environmental data almost as it happens, tomorrow's pharmaceutical supply chain is going to be about acting rather than reacting.

## Fridge-tag® 3 for Storage Monitoring

The Fridge-tag® 3 is mainly designed to monitor refrigerators, freezers or the smaller stockrooms of pharmacies (2-8 or 15-25 °C) See video at http://www.berlinger.com/en/temperature-monitoring/training-support/videos/fridge-tag-3-videos/

With the Fridge-tag® 3 it is possible to intervene quickly in the event of a temperature infraction to prevent expensive product wastage, ensure product safety and maintain regulatory compliance. It is a robust RTM device/system which transmits via an international SIM card. A key benefit of the Fridge-tag 3 design is that it will continue to function and transmit data in the event of a power loss. This is generally not the case with other devices using wi-fi. Even in total communication system failures, the device collects and stores data for up to sixty days and this can be accessed without need for special software.

With the Fridge-tag® 3 device from Berlinger, notifications are possible in real-time via SMS, an easy to hear signal or via a web portal. The device works as a standalone and, unlike Bluetooth wireless technology, does not rely on pairing with another device. Proactive action is made easy with the Fridge-tag® 3, as it automatically sends alarm messages when min/max temperatures between -40 °C and + 60 °C are exceeded or fail to be met (depending on configuration).

### Immediate, quick and reliable

To alert QA staff in critical situations such as an unexpected temperature rise or in a refrigerator or to warn technicians in the event of a fault (e.g. power failure) affecting system integrity, an immediate alert appears directly on the mobile phone of the responsible person(s). With Fridge-tag® 3, notifications are available in real-time via SMS and the smartview® web platform for centralised monitoring.

### Simple to operate

The programming of the range of alarms on the Fridge-tag® 3 can be easily carried out via a simple SMS text command. Up to five destination numbers can be recorded in the alarm/warning relay. No matter where you are at any given moment, an immediate alarm is ensured and querying the temperature is possible at any time and from anywhere via SMS. The data that is collected can be accessed and analysed via a display, PDF report (no software needed) or through a smartview® or other cloud-based control center. The Fridge-tag® 3 can be ordered with an optional external temperature sensor with direct cable linkage for maximum data security.

## Wireless Facility and Transport Monitoring with smartLine

In addition to the Fridge-tag® 3, Berlinger also offer the wireless smartLine system tailored for monitoring bigger facilities/cold rooms and for monitoring vehicles. More information can be found at www.berlinger.com/smartline

### Do you really need all those sensors?

It may seem sensible to select a logger that offer sensors for measuring a number of different variables. However additional features eat into battery life and can add unnecessary complexity. This can make them harder to configure, harder to calibrate and require more training to operate.

### The "Best Systems"

According to some experts "the best systems for the in-transit monitoring of sensitive drug products are those systems which have resulted from a close partnership between the shipper and its suppliers; one where the result is an optimum combination of protection, performance and cost for the risks concerned."(8). An ideal temperature management system will encompass compatible monitoring solutions dealing with all aspects of cold chain monitoring from primary cold storage facilities to cargo transportation and temporary cold stores.


# Choosing a Data Logger

UNICEF in their guidance for selecting temperature-monitoring equipment guidance(27) recommend that users "ensure that reliable temperature monitoring devices are chosen that are fit for purpose and that, wherever possible and available, are World Health Organization (WHO) Performance, Quality and Safety (PQS) pre-qualified."

## About WHO PQS

The WHO Performance, Quality and Safety (PQS) process pre-qualifies products and devices so that member states and UN purchasing agencies are assured of their suitability for use in immunization programs.

The WHO PQS approach to equipment and device pre-qualification is based on three key criteria: a selected product must have performance characteristics that meet the relevant specification standards; quality and reliability characteristics that are appropriate for field conditions, and cradle-to-grave safety characteristics that ensure that no harm is caused to users, patients, or to the environment over the course of the product's life cycle. All products are subject to a formal annual review process which takes place in April each year.

## Check-List

Factors that need to be considered when choosing a real-time temperature monitoring device include:

- Reliability MTBF
- Immediacy
- Accuracy
- Readability
- Durability
- Ease of use
- Flexibility in use
- Dimensions
- Standalone operation/cloud/both
- Data transfer interface and ease of transfer - Wireless, USB
- Software options
- Certifications/approvals
- Auto-upgrade capabilities - future-proof software/technology
- Non-volatile memory capacity
- Measuring range
- Tamper-proof features
- Data security features - encryption, password protection etc.
- Platform compliancy
- Reporting compliancy
- Configurability
- Customisable alarm capabilities
- Analytic capability
- Ease of calibration / pre-calibrated
- Service life expectancy
- Battery
    - Size/power consumption/life
    - Rechargeable/time to charge
    - Fast charge capability?
    - Replaceable?
- Sensor array/options
- Sampling rates – configurable measurement time intervals
- Price

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