Best-Practice Guide
Pharmaceutical-Chain Temperature Control and Recording

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ABB

Introduction

Medicinal products require controlled storage and transit conditions in order to ensure that their quality is not compromised. This applies to low-risk products as well as high-risk products such as vaccines, insulins and blood products (such as Factor VIII), which normally require storage between 2°C and 8°C. All distributors of drug products are required to record storage and transportation temperatures, as well as being licensed by the appropriate authorities. Temperature monitoring devices should be used to demonstrate compliance with the records that are kept.

The pharmaceutical distribution chain

At every point in the chain, precautions should be taken to minimise the effect of external conditions on the quality and stability of the product. It is mandatory that records should provide reliable up-to-date evidence of compliance, incase of audits and investigations from the MHRA and other stakeholders. Before setting up a storage facility, transport system or taking on a new range of products it is advisable that distributors carry out a risk analysis.

This guide offers you knowledge and advice on best practice throughout the distribution chain, including storage and transportation.

Cold storage

Low volume

Domestic refrigerators may be suitable for cold storage of small volumes of some products, for example eye drops, which require cold storage but are less susceptible to being out of the recommended temperature range.

Domestic refrigerators:

- Are generally not suitable for high-risk products
- May not have the precise electronic control necessary to maintain the temperature within the range 5°C±3°C

The minimum requirement for monitoring is a max/min thermometer. This should be placed within the load and positioned so that opening and closing the door will not affect the readings. The thermometer should be read and reset daily and the maximum and minimum temperatures recorded. Care should be exercised when placing goods in domestic units. If placed next to or in contact with the chiller plate or coil, their temperature may fall below the recommended minimum. Because domestic refrigerators lack the precise temperature control and uniformity, continuous recording should be considered. Thermal mapping is also advisable to determine cold and warm locations over a period of time.

High-risk products

- The refrigerator must be capable of maintaining the temperature of its contents between 2°C and 8°C throughout its volume, with the minimum of intervention
- Temperature monitoring should be performed by an electronic max/min thermometer with an accuracy of + 0.5°C, and should be readable from outside the refrigerator. Continuous, independent, recording with alarms would normally be advised
- It is advised that the thermometer should have a battery back-up (if mains powered) so traceability of product temperature can be maintained should the power fail
- The probe should be placed within the load (or within a suitable buffer) to record the load rather than the air temperature, and the max/min temperatures should be recorded daily to ensure that the refrigerator remains within its specifications

- The device should be calibrated annually against a certificated thermometer and should be temperature mapped
- The unit should have an auto-defrost facility and the temperature of product within the unit should not fall outside defined limits during the defrost cycle
- Refrigerators should be sited in an environment where the ambient temperature does not affect the temperature control within the unit. This normally means an external environment of between 10°C and 32°C

High volume

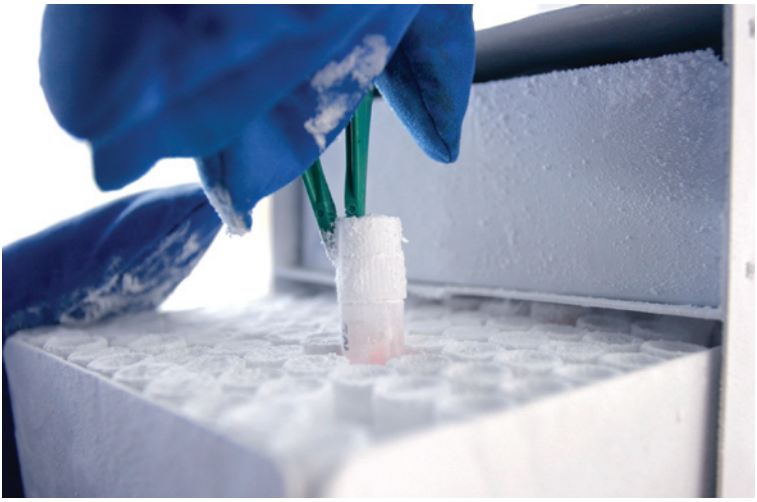
Large refrigerators (in excess of 6 m^3) and walk-in cold rooms used in high-volume operations should be fitted with an electronic temperature-recording device that measures load temperatures. The chart, printout or direct reading should be checked daily and the examination recorded, either in a logbook or by annotation of the record chart or print-out. The use of electronic recorders should be considered.

- The facility should be fitted with a power-failure alarm
- Portable data-loggers, which can be downloaded onto a computer, may be used instead of a fixed device, though the system should allow temperatures to be seen/alarmed at all times
- The internal air temperature distribution should be mapped on installation in both the empty and full state. Air temperature distribution should be checked annually under conditions of normal use
- External conditions should be taken into consideration during mapping
- The recorder probe should be placed within the load for routine monitoring and if air distribution is not fan-assisted the probe should be located in the part of the load at the highest risk from low temperatures. Consideration should be given to the use of multiple probes placed as required with reference to the temperature mapping results

Walk-in units

- Temperature mapping should be repeated if significant changes take place, such as the repair or replacement of the refrigeration unit or changes to the internal storage layout
- A calibrated max/min thermometer should be placed inside the unit for use as a back-up and to confirm the temperature indicated on the recorder

- Goods sensitive to temperatures greater than 8°C should not be stored next to the door and goods susceptible to temperatures below 2°C should not be placed in the airflow from the refrigeration unit
- Probes should be sited within an appropriate load simulator so that transient rises in temperature (such as might occur when a door is opened) do not trigger the alarm
- The low-temperature alarm must trigger before the temperature drops below +1°C
- Condensate from chiller units should not be collected inside the cold store in an open vessel
- Consideration can be given to the monitoring of relative humidity (RH) within the facility
- Large refrigerators and walk-in units should be subject to regular (at least annual) servicing



Freezers

A small but increasing number of products must be stored frozen (e.g. some blood products and products of biotechnology). These will be labelled store below -5°C (freeze) or below -15°C (deep freeze) or they may show a range (e.g. -15°C to -20°C). Storage units must be capable of maintaining the required temperature in all parts of the load, and temperatures should be monitored within the load and recorded daily.

Transporting products that require low-temperature storage

The type of shipping system will be decided by the load size, the nature of the product, the risk presented by high and low temperatures and fluctuations, and the time of exposure to adverse conditions.

- Bulk cold-chain goods should preferably be shipped in refrigerated transport
- Refrigerated vehicles are appropriate for distribution of smaller consignments of high-risk goods, such as vaccines; temperature should be strictly monitored
- Temperature-stabilising materials should be chosen with care. Dry ice should not be used in shipping rubber-stoppered vials because the low temperature may lead to shrinkage of the rubber
- Refrigerated vehicles should be fitted with continuous recording devices, or a number of portable monitoring devices may be placed within the load
- The number of temperature monitors will depend on the size of the load and they must be located carefully to ensure temperatures in all parts of the load remain acceptable
- The temperature gradient within a large load can vary significantly from outside to middle
- Shipping companies and distributors should review temperature records for each consignment and have a procedure in place for implementing corrective action in the case of adverse events
- For smaller consignments transported by road in individual thermal containers, where transit times are measured in hours rather than days, it may be possible to rely on validation data supported by occasional temperature monitoring of deliveries
- Distributors should ensure that recipients of cold-chain goods are aware that the consignment contains goods which require special storage conditions
- Suppliers should indicate clearly on the packaging both when the product was removed from cold storage and when it must be placed back
- The consignee is advised to satisfy himself that the goods have not been subjected to adverse conditions during transit. For example, by viewing a printout from a data logger or monitoring device placed in the load by the consignor
- Consignors should provide a clear diary of the journey

Returns

Returns of high-risk goods should be accepted for reissue only if the customer notifies the distributor of the error immediately on receipt of the goods, and it can be demonstrated the goods have been held under suitable conditions (e.g. by signed copy of a recorder chart).

Returns of lower risk goods may be acceptable, provided that they are made promptly and that it can be established that they have not been outside cold storage for a total of more than 24 hours.

Cool storage

A small number of medicinal products are labelled ‘store in a cool place’ or ‘store between 8°C and 15°C’. If a facility operating within this range is not available, advice is that the goods may be stored at 2°C-8°C, provided that storage below 8°C does not affect their physical stability. Otherwise they should be stored in the coolest part of the warehouse and temperature monitoring should be regularly carried out.

Controlled room temperature storage

Unless stated otherwise, the majority of medicinal products can be stored under conditions of controlled room temperature. These products are usually labelled ‘do not store above 25°C’. For these products room temperature extremes of hot and cold temperature must not be encountered.

The minimum requirement for temperature measurement is that a max/min thermometer be placed at a strategic location and read, recorded and reset regularly and measured at both low and high levels. During periods of exceptionally hot or cold weather the frequency of monitoring should be increased. Warehouses should be temperature mapped to determine the temperature distribution.

Mapping should be repeated every 2-3 years and after any significant modification to the premises, stock layout, or heating system. Heat gain of goods stored next to sun-facing windows, at high level in poorly insulated stores, or next to heaters, should be considered.

Mean Kinetic Temperature

MKT is a calculated fixed temperature that simulates the effects of temperature variations over a period of time. It expresses the cumulative thermal stress experienced by a product at varying temperatures during storage and distribution. Good warehousing and distribution practice requires that warehouse temperatures are controlled and monitored and that appropriate action is taken if temperatures exceed the storage conditions stated on product labels.

- Strict conditions should be applied to the use of MKT
- It is applicable only to the storage of products under controlled room temperature conditions, such as those labelled 'do not store above 25°C'
- The application of MKT should be described in a written procedure
- MKT should not be used to compensate for poor temperature control of storage facilities
- The calculation of MKT for the time that a product has been in storage can only be carried out off-line as any on-line calculation can only be for the entire storage facility

Calibration of measuring devices

Manual and electronic measuring and recording devices used in critical areas and with high-risk goods should be calibrated at least annually against a traceable reference device. Records should include pre- and post- calibration readings and details of any adjustments made.

Written procedures and records

Written procedures should be available to describe the control and monitoring of storage and transportation temperatures and the calibration of measuring devices. Procedures should include alert and action alarm limits and the procedure to be followed if the temperature falls outside these limits. The designated responsible person should review monitoring records independently, at least monthly, if this person is not involved directly with the day-to-day monitoring. This review should be recorded.

- Consider a risk assessment of the storage facilities
- Consider the number of monitoring points against volume and thermal mapping results
- Consider backup power supply to ensure continuous monitoring during power/plant failure
- Remember each storage facility requires to be temperature logged
- Consider the cost/benefit of continuous monitoring against manual recording
- Ensure that temperature recording remains valid with regular thermal mapping and instrument calibration
- Self inspections should be carried out and recorded
- Consideration can be given to the use of a central monitoring recorder with probes located at different facilities. A risk analysis should be performed

References:

MHRA Guidance Note No.6: NOTES FOR APPLICANTS AND HOLDERS OF A WHOLESALE DEALER'S LICENCE

Recommendations on the control and monitoring of storage and transportation temperatures of medicinal products: John Taylor, CChem, FRSC.

MHRA website: www.mhra.gov.uk

Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03):

http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2001/may/gdpguidelines1.pdf

ABB instrumentation

We have the knowledge and solutions to help you reach optimum temperature control throughout the pharmaceutical distribution chain. We offer a range of video graphic recorders, controllers, services and software solutions to work alongside you. Profit from data.

ABB solutions

SM500F

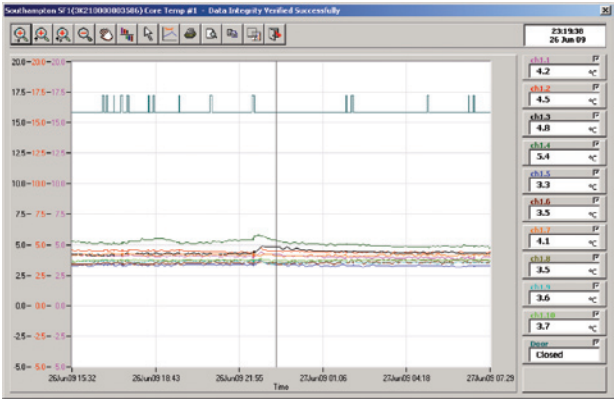
The world's first field-mountable video graphic recorder takes recording out of the control room and offers local access to operational data. The SM500F is a four-channel recorder that can be installed even in the most hostile environments. It helps users protect their operational critical activities, while providing reduced costs of ownership compared to paper chart recorders.

SM3000

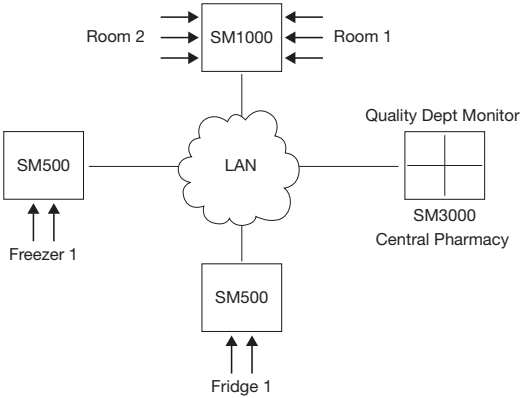
Multipoint process monitoring made simple. With the SM3000 up to 36 channels can be recorded. The large 31cm bright, clear display maximises the visibility of process data and allows the use of a wide variety of displays.

DataManager

Analysis of process data archived by an SM series recorder can easily be performed using DataManager advanced analysis software. In addition to charting process data and the validation of file security, DataManager provides management of all data files and historical logs archived from any number of recorders.



Typical results from Data Manager Software Archive Viewing Tool



Typical facility monitoring/recording architecture

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