# Recommendations on the control and monitoring of storage and transportation temperatures of medicinal products

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## 1. Introduction

Medicinal products, and starting materials used in the manufacture of medicinal products, should be stored and transported under conditions which ensure that their quality is maintained. Manufacturers' recommendations concerning storage temperatures should be observed and this may involve the use of specialised storage and transport facilities. Temperature-monitoring devices should be used to demonstrate compliance with the designated temperature ranges.

The distribution chain is seldom simple and distribution systems may vary enormously. In its simplest form, the chain involves shipment direct from the manufacturer to the customer or end user. In its more complex form, the distribution chain may involve a number of storage and transit locations, including airports and docks, and a variety of transport facilities, including aircraft.

Good warehousing and distribution practices[1] require that storage areas for medicines should be maintained within acceptable temperature limits and that, where special storage conditions are specified by the manufacturer, these should be provided, checked and monitored. Measuring and monitoring equipment should be calibrated and checked at defined intervals. Medicinal products should be transported in such a way that they are not subjected to unacceptable degrees of heat and cold, and specialised means of transportation should be used where necessary.

There have been a number of open seminars and conferences on this subject in recent years. The Medicines Control Agency (MCA) has published guidelines for the pharmaceutical industry[2] and the British Association of Pharmaceutical Wholesalers has introduced a protocol for its members[3]. This paper provides additional advice for the control and monitoring of temperatures during the storage, shipping and distribution of medicinal products.

## 2. Controlled low temperature storage

### 2.1 The cold chain

The cold chain involves all of the storage and transport facilities necessary to ship a product requiring controlled low-temperature storage from the manufacturer to the end user. In some circumstances (such as the manufacture of a product containing a temperature sensitive active ingredient) the cold chain may also include the storage and shipping of active pharmaceutical ingredients used in the manufacture of the product. At every point in the chain precautions should be taken to minimise the effect of adverse external conditions on the quality and stability of that product. Where relevant, records should be maintained to provide evidence of compliance with the labelled storage recommendations for those in whose care the product is at

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the time and to other interested parties who may seek this assurance, such as the recipient and/or marketing authorisation holder.

There is an increasing number of medicinal products requiring controlled storage and transit conditions. Among the cold-chain items are high-risk products such as vaccines, insulins, blood products (such as Factor VIII) and other proteinaceous materials, which normally require storage between 2ºC and 8ºC. These products must be protected from freezing; even a brief period at sub-zero temperatures may irreversibly denature the protein, leading to a loss of efficacy. There are also products such as emulsion systems and solutions of sparingly soluble components which may become physically unstable at sub-zero temperatures.

Before setting up a cold storage facility or transport system, or before taking on a new range of products, it may be useful for distributors to carry out a risk analysis to establish a list of high, medium and low risk products and to make apropriate arrangements for their handling.

## 2.2 Cold storage

### 2.2.1 Low-volume operations

Domestic refrigerators may be suitable for cold storage of small volumes of some medicinal products, for example eye drops which require cold storage but which are less susceptible to brief minor excursions outside the recommended temperature range than the high risk products referred to above. Domestic refrigerators are generally not suitable for high risk products because they may not have the precise electronic control necessary to maintain the temperature within the range 5±3ºC. Refrigerators are available which are specially designed for the storage of medicinal products and their use is to be encouraged for all products requiring storage between 2°C and 8°C.

The minimum requirement for temperature monitoring is for a thermometer which measures maximum and minimum temperatures to be placed within the load, so that as far as possible it is not affected by repeatedly opening and closing the door. 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 they are placed next to, or allowed to come into contact with the chiller plate or coil, their temperature may fall below the minimum recommended by the manufacturer. This is particularly relevant in the case of high-risk products. Sufficient space should be maintained between the goods and the internal surfaces of the unit to permit adequate air circulation, but if the unit is regularly filled to capacity, the effect on temperature distribution should be investigated.

For high-risk products, the refrigerator must be capable of maintaining the temperature of its contents between 2°C and 8°C, with the minimum of intervention. Temperature monitoring should be by electronic max/min thermometer, with an accuracy of ± 0.5°C, which should be readable from outside the refrigerator. It is advised that the thermometer has a battery back-up (if mains powered) so that it will continue to function for 48 hours in the event of a power failure. 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. The device should be calibrated annually against a certificated thermometer. The unit should

have an auto-defrost facility and the temperature within the unit should not be affected during the defrost cycle. If an alarm is fitted, the correct functioning of the alarm should be checked annually at the high and low set points. It is preferred that a power failure alarm be fitted and that the thermostat which controls the chiller unit should fail safe - i.e. the temperature does not decrease if the thermostat fails.

Refrigerators should be sited in an environment where the ambient temperature does not affect the temperature control within the unit. For example, it should not be sited in an unheated loading bay, or in an area of potential heat gain. Most refrigerators will function efficiently in an external environment of between 10°C to 32°C.

### 2.2.2 High-volume operations

Large refrigerators (in excess of 6 $m^3$) and walk-in cold rooms used in high volume operations should be fitted with a suitable electronic temperature-recording device which measures load temperature(s). The chart, print-out or direct reading should be checked daily and the examination recorded, either in a logbook, or by annotation of the chart/print-out if appropriate. The recording device should continue to function for 48 hours in the event of a power failure; the facility should be fitted with a power-failure alarm. Portable data-loggers which can be down-loaded onto a computer may be used instead of a fixed device.

For large refrigerators and walk-in units, the internal air temperature distribution should be mapped on installation in the empty and full state. Thereafter air temperature distribution should be checked annually under conditions of normal use. External conditions should also be taken into consideration during mapping, as extremes of environmental temperatures may adversely affect the performance of the cooling/heating units to the extent that the may become ineffective. 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 that part of the load which is at the highest risk from low temperatures. It is preferable that the recorder probe is independent of the temperature-controlling probe. The auto-defrost facility should not affect the temperature during the defrost cycle.

For 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. It is preferable that multiple probes are used for routine temperature monitoring, but if only one is fitted it should be sited in a location where the temperature is representative of the load in general, as indicated by the mapping exercise. A calibrated max/min thermometer should be placed inside the unit for use as a back-up in case of failure of the electronic monitoring system and to confirm the temperature indicated on the recorder. For walk-in units, it is less important that the load temperature rather than the air temperature be monitored, because the temperature variation caused by opening and closing the door is of less significance provided that it is not left open for prolonged periods. As a general rule, goods particularly sensitive to temperatures > 8°C should not be stored next to the door and goods susceptible to temperatures < 2°C should not be placed in the airflow from the refrigeration unit. Recording probes should preferably be independent of controlling probes.

High/low temperature alarms should be fitted and suitable limits set. Probes should be sited within an appropriate load simulator so that transient rises in temperature (such as migh occur

when a door is opened) do not trigger the alarm. In order to minimise false alarms it may be possible to set a time delay on the system to allow for controlled periods for stocking and picking. The low temperature alarm must trigger before the temperature drops below +1°. Alarms should be tested regularly throughout the year. It should be remembered that an alarm is of little use if there is nobody to hear and respond to it; provision must be made for out-of-hours response.

Condensate from chiller units should not be collected inside the cold store in an open vessel.

Large refrigerators and walk-in units should be subject to regular (at least annual) servicing. Routine servicing should include calibration of the recording and alarm systems. All units, large and small, should be cleaned and disinfected regularly to prevent mould growth, and (as for all storage facilities) goods should not be stored directly on the floor.

#### 2.2.3 Open-fronted units

Temperature distribution within open-fronted units of the type found in food stores can be difficult to control and their use for routine storage of medicinal products should be avoided. These units may be acceptable for short-term storage of picked goods awaiting despatch, provided that it is demonstrated that freezing conditions do not occur. A probe should be fitted to confirm that such conditions do not occur.

#### 2.2.4 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 -5º (freeze) or below -15º (deep freeze) or they may show a range (e.g. -15º to -20º). Storage units must be capable of maintaining the required temperature in all parts of the load and load temperatures should be monitored and recorded daily. The units should be routinely maintained and temperature probes calibrated. Goods should be transported in such a way that the maximum recommended storage temperature is not exceeded.

### 2.3 Transporting products which require controlled low temperature storage

For any given time of the year, the distribution environment can vary markedly from country-to-country and within countries. The environment will also change significantly according to the season and all of these variables should be taken into consideration in cold-chain distribution. Except for relatively short transit times and journeys within the same climatic area, it is virtually impossible to validate a shipping system against all conditions which might be encountered. The type of shipping system selected will be governed by the load size, the nature of the product to be shipped, the risk presented by high and low temperatures and temperature fluctuations (particularly alternate freezing and thawing) and the time of exposure of the system to adverse conditions. Bulk cold-chain goods should preferably be shipped in refrigerated transport if transit times are prolonged. Refrigerated vehicles are also appropriate for distribution of smaller consignments of high-risk goods, such as vaccines, particularly where there may be a number of drop-off points and where transit times are in excess of three hours. Where small volume deliveries of these goods involving short (< 3 hours) transit times

are made to individual customers by wholesalers, insulated packaging without cooling elements may provide adequate protection.

A number of container systems have been developed and evaluated for protecting temperature-sensitive medicines during shipment. These are constructed of thermal insulating material and contain compartments or baffles to separate products from temperature-stabilising materials (such as eutectic plates or ice packs). It is vital that products denatured by freezing are prevented from coming into direct contact with ice packs at sub-zero temperatures. 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 with subsequent ingress of (unsterile) air and carbon dioxide. Refrigerated vehicles or thermal container systems designed to protect products from elevated temperatures may also protect products from freezing in sub-zero external environments.

Temperatures within loads of high-risk products should be strictly controlled and monitored. Refrigerated vehicles should be fitted with continuous recording devices, or, alternatively, 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 provide assurance that temperatures in all parts of the load remain acceptable. The temperature gradient within a large load can vary significantly from outside to middle and can be greatly influenced by external temperatures if the container or vehicle is not well insulated. 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. Shipping companies should carry out a regular review of their operations to confirm that they remain capable of maintaining the quality of the products which they handle.

For smaller consignments transported by road in individual thermal containers, where transit times are measured in hours rather than days and where journeys are within the same climatic area and extremes of temperature are not the norm, it may be possible to rely on validation data supported by occasional temperature monitoring of deliveries to provide the necessary assurance of product protection. Where airfreight is used, each consignment should be monitored.

Distributors should ensure that recipients of cold-chain goods are aware that the consignment contains goods which require special storage conditions, for example by applying warning labels to outer packaging (e.g. COLD CHAIN PRODUCT). The consignee should ensure that these goods are removed to the appropriate storage facilities as soon as possible after receipt and always within two hours. Where relevant, suppliers should indicate clearly on the packaging both when the product was removed from cold storage and the latest date/time when it must be placed back into cold storage. The consignee is advised to satisfy himself that the goods have not been subjected to adverse conditions during transit and this could be done, for example, by sight of a printout from a data logger or monitoring device placed in the load by the consgnor. Consignors should also provide a clear diary of the journey. It is good practice for consignees to check the temperature in various parts of the consignment using a hand-held electronic thermometer.

Technical agreements should be drawn up to describe arrangements and responsibilities between contract givers and contract receivers in respect of contract warehousing and distribution. Contract givers should audit their proposed contractors before establishing an

agreement and re-assess from time-to-time their ability to provide a service of the required quality.

### 2.4 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 he is able to demonstrate to the distributor that the goods have been held under satisfactory conditions (e.g. by signed copy of a recorder chart) between receipt and collection. Collection should normally be done by the distributor, preferably using refrigerated transport. 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. In these cases the susceptibility of the product to out-of-specification storage conditions should be considered and return to stock justified and documented by the Qualified Person or Responsible Person, as appropriate.

### 2.5 'Cool' storage

A small number of medicinal products are labelled 'store in a cool place' or 'store between 8°C and 15°C'. If these requirements are encountered, and a facility operating within this range is not available, advice is that (preferably) the goods may be stored at 2ºC-8ºC if space permits, provided that storage below 8ºC does not affect their physical stability. Otherwise they should be stored in the coolest part of the warehouse compatible with good practices (e.g. not in the loading bay) provided that it is not excessively warm - temperatures > 18°C would not be appropriate. Temperature monitoring should be carried out and stock should not be allowed to accumulate; turn-over should be rapid. If distributors are in any doubt over their handling of these products, they should seek the advice of the appropriate marketing authorisation holders.

The MCA recognises that these storage requirements are not convenient for many distributors and is encouraging licence/authorisation holders to provide data to vary storage requirements in line with the recommendations of the International Conference on Harmonisation (ICH). For example, "Do not store above 25ºC" or "Store at 2-8ºC [5].

## 3. Controlled room temperature storage

Unless stated otherwise in product literature and labels, the majority of medicinal products can be stored under conditions of controlled room temperature without compromise to their stability and recommended shelf-life. These products are usually labelled 'do not store above 25°C' (or for some products 'do not store above 30°C'). "Controlled" room temperature is used to imply a degree of control over the temperature of the storage environment, such that extremes of hot and cold temperature are not encountered. "Room temperature" and "ambient temperature" are not acceptable terminology for labelled storage recommendations.

The extent of temperature monitoring necessary for the storage of these products will depend upon the size of the facility. The minimum requirement is that a max/min thermometer be

placed at a strategic location and read, recorded and reset regularly, at a frequency determined by a knowledge of the stability of the ambient temperature, but at least weekly. With the exception of very small stores, temperatures should normally be recorded at both low and high levels. During periods of exceptionally hot or cold weather the frequency of monitoring should be increased. Continuous temperature recording is recommended for large warehouses. Self-contained storage areas within warehouses, (e.g. CD store, flammables store) should be included in temperature monitoring programmes.

Warehouses should be temperature mapped to determine the temperature distribution under extremes of external temperature. Mapping should be repeated every 2-3 years and after any significant modification to the premises, stock layout, or heating system. Due consideration should be given to conditions which may arise if heating systems are shut down overnight or over weekends. Heat gain of goods stored next to sun-facing windows, at high level in poorly insulated stores, or next to heaters, should be considered. Medicines must not be stored in areas shown by temperature mapping to be unsuitable.

The temperature of goods distributed in non-insulated transport is affected significantly by external temperatures. There will be significant heat gain inside unventilated steel-bodied delivery vehicles in sunny conditions and precautions should be taken where necessary to protect goods from heat challenge. In addition to affecting chemical stability, elevated temperatures may affect physical properties, for example causing separation of emulsion systems and sedimentation of active ingredients in suspensions and suppositories. Likewise, low external temperatures may cause components to crystallise or separate from liquid medicines. External temperatures are an important consideration in the use of postal services for distribution of medicines; temperatures as high as 60°C were measured in mailboxes in the USA during a study of temperature excursions occurring during mail-order shipment[4].

External temperatures may have a significant effect on the stability of representatives' samples kept in car boots and suitable precautions should be taken to protect these goods, for example by minimising the time for which they are held, keeping them in suitable insulated containers and removing them from vehicles overnight.

## 4. Mean Kinetic Temperature

The ICH stability testing guideline[5] defines mean kinetic temperature (MKT) as 'a single derived temperature which, if maintained over a defined period, would afford the same thermal challenge to a drug substance or drug product as would have been experienced over a range of both higher and lower temperatures for an equivalent defined period'. In other words, 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. It is not unusual to find that warehouse temperatures exceed the recommended maximum storage temperature of 25°C occasionally during summer months, even in those warehouses which have sophisticated building management systems. Where maximum temperatures for goods requiring controlled room

temperature storage do not exceed 30°C and when the number of excursions above 25°C is relatively small, the concept of MKT may be applied in order to provide assurance that the actual storage conditions will not affect adversely the stability and shelf life of the products.

The formula for calculation of MKT is based on the Arrhenius equation:

$$T_k = \frac{\Delta H/R}{-\ln \dfrac{e^{-\Delta H/RT(1)} + e^{-\Delta H/RT(2)} + \ldots\ldots\ldots e^{-\Delta H/RT(n)}}{n}}$$

$T_k$ is the MKT, $\Delta H$ is the activation energy, R is the universal gas constant, T is the temperature in degrees K (i.e. °C + 273.1) n is the total number of (equal) time periods over which data are collected and *e* is the natural log base.

The practical application of this equation is less complex than it first appears. $\Delta H/R$ is a constant (9982.68) $T_{(1)}$ is the average temperature recorded over the first time period and $T_{(n)}$ is the average temperature recorded over the nth time period. A simple way to apply MKT is to calculate the mean of the measured maximum and minimum daily temperatures for seven days (the time period) - this average temperature, plus 273.1°, becomes $T_{(1)}$ in the equation. The mean over the next seven days becomes $T_{(2)}$ and so on. If MKT is to be calculated over a four-week period, n is 4.

In order for MKT to be meaningful, there should be an appropriate number of temperature/time sampling points. Temperature monitoring should be carried out daily and MKT calculated on at least a monthly basis to provide the necessary assurance of temperature control. Some building management systems will calculate average daily temperatures using a large number of data points (rather than one maximum and one minimum temperature measurement each day from manual monitoring). These can be used, together with a computer programme, to calculate MKT on a weekly or monthly basis with a greater degree of accuracy.

Strict conditions should be applied to the use of MKT. It is applicable only to storage of products under controlled room temperature conditions (i.e. those labelled ‘do not store above 25°C’). MKT can be applied to the shipping of these products and it may provide a degree of assurance during prolonged transit periods. MKT is not appropriate for products requiring controlled low temperature storage and shipping.

The application of MKT should be described in a written procedure. This should include the positioning, reading and calibration of temperature monitoring devices, the frequency of temperature recording, action and alert limits for temperatures, the frequency of calculation of MKT and action to be taken in the event of an out-of-limit temperature reading or calculated MKT value. The maximum limit for MKT for a product requiring storage at or below 25°C is 25°C, which allows for storage temperature excursions of between 15°C and 30°C. Actual

storage temperatures should not exceed 30°C if MKT is to be applied and the number of excursions permitted above the labelled maximum temperatures should be limited and consistent with good warehousing and distribution practice.

MKT should not be used to compensate for poor temperature control of storage facilities. It may be applied in situations where control is relatively good, but where occasional excursions may be encountered.

## 5. Calibration of measuring devices

Manual and electronic measuring and recording devices which are used in critical areas (e.g. temperature monitoring of storage and transport facilities for high-risk cold-chain 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 or corrections to be applied. Alarms should be checked for correct functioning at the designated set points.

## 6. 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 limits and the procedure to be followed if the temperature falls outside these limits.

The designated Responsible Person (or his/her nominee) should review monitoring records independently at least monthly, if this person is not involved directly with the day-to-day monitoring. The review should be recorded. Review of records should be included in the programme of self-inspection.

## 7. Training

Appropriate training should be provided for all staff involved in the distribution of medicinal products, including delivery drivers. Each employee should receive a general introduction to good distribution practice and this should be supplemented by training relevant to his/her specific responsibilities. There should be a written procedure for each operation that has an influence on product quality and training should be given in the application of the procedures. Procedures concerning temperature monitoring should include the frequency of monitoring, location of recording devices, acceptable temperature limits for the various storage areas, records, calibration of monitoring devices, temperature mapping, alarms and action to be taken in the event of a temperature excursion.There should be a written procedure which describes the training programme and training records should be retained for each employee.

## 8. Humidity

Given that adequate protection is afforded by primary packaging materials, the effects of high relative humidity on the stability of medicinal products during storage and distribution is

relatively insignificant. However, humidity can have a deleterious effect on the strength of secondary cardboard packaging. Cartons stacked in environments where the RH is high (such as in cold stores or in refrigerated transport) may become softened and collapse, exposing their contents to risk of damage from physical shock. Where products are required to be stored under specified conditions, relative humidity must be monitored and recorded.

## 9. Conclusions

By following the advice given in this paper, the result of inspection experience and discussion with industry, distributors will help to maintain the quality of medicinal products which they handle and thus contribute to the safety and effectiveness of medicines and the well-being of patients. Inspectors will bear these recommendations in mind when assessing the arrangements of manufacturers and wholesalers.

## 10. References


[1] Guidelines on good distribution practice of medicinal products for human use (94/C 63/03)

[2] The Control and Monitoring of Storage and Transit Temperatures: Medicines Agency Information Letter (MAIL) No. 99, January/February 1997.

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