HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances

IA-G0011-3
2 OCTOBER 2020
This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.

CONTENTS

1 INTRODUCTION

The purpose of this document is to provide guidance to human and veterinary medicinal product manufacturers, wholesalers and transporters of human medicinal products in Ireland and manufacturers of active pharmaceutical ingredients (APIs) in relation to conditions for cold storage/cold-chain and controlled temperature storage.

Special storage conditions for active substances should be based on results from stability studies.

The storage conditions for medicinal products should also be based on the results of the stability studies undertaken on the finished product.

Stability testing is necessary to ensure the product is of acceptable quality throughout its entire storage period. In order to do this, it is necessary to monitor compliance of the product with a suitable quality specification throughout the shelf life.

The shelf life is defined by ICH as 'the time period during which a drug product is expected to remain within approved shelf-life specification, provided that it is stored under the conditions defined on the container label.'

The following are examples of specific storage statements that are declared on the label of a medicinal product:

- Do not store above 25°C/Do not store above 30°C
- Store below 25°C/Store below 30°C
- Store in a refrigerator (2°C – 8°C)
- Store and transport refrigerated (2°C – 8°C)
- Store in a freezer (temperature range)*
- Do not refrigerate/Do not freeze

  (*Freezer storage temperatures may vary from 0°C to -20°C or below -20°C)

Products should be stored according to conditions described on the label.

For many medicinal products, storage and transportation temperatures are a highly significant factor in maintaining the quality of medicinal products throughout the distribution network. The distribution chain is seldom simple and distribution systems can vary enormously. In its simplest form, the chain involves shipment direct from the manufacturer to the customer or end user but, in reality, the chain is rarely this short. In its more complex form, the distribution chain may involve a number of storage and transit locations, including airports, docks, and a variety of methods of transport, including aircraft.

Recommendations concerning storage temperatures given on product labels and in product literature are made to ensure optimum quality of the products throughout their shelf life. One of the requirements of the marketing authorisation (MA) is that the storage conditions for the

products are met. Monitoring of temperatures in storage facilities and during transportation using calibrated measuring devices is necessary in order to provide assurance that conditions are under control, and specialised facilities may need to be acquired to ensure that product quality is maintained.

The effect of elevated temperatures on the chemical stability of medicines is well recognised but elevated temperatures can also have an adverse effect on the physical properties of some formulation types. For example, separation of emulsion systems and sedimentation of active ingredients in suspensions and semi-solids are among the changes that can occur. Products based on emulsion systems and solutions of sparingly soluble components may also become physically unstable at sub-zero temperatures.

An increasing number of medicinal products require controlled storage and transportation conditions of between 2°C and 8°C. Some of these, for example vaccines, insulin and products of biotechnology, must be protected from freezing. Even a brief period at sub-zero temperatures may irreversibly denature protein and lead to a loss of efficacy, and therefore such medicinal products must be maintained within a narrow temperature range above freezing point throughout the distribution chain.

A large number of medicinal products have storage indications which state, e.g. 'Do not store above 25°C', 'Do not refrigerate'.

For the purposes of this document, 'controlled temperature storage' is defined as the storage requirements for products not requiring cold storage or freezing.

Conditions within the distribution chain can vary markedly at different times of year. The environment also changes significantly according to the season and all of these variables have an influence on cold-chain distribution. Validation studies can provide an adequate level of assurance. Hence, validation is required in order to assess the worst-case conditions.

This document details the controls that must be put in place by manufacturers, wholesalers, distributors and transporters of these products to ensure continuity of the 'cold-chain' while these products are in their care and also details the requirements for controlled temperature storage.

To summarise, medicinal products should be stored and transported under conditions which ensure that their quality is maintained. To ensure that products are stored correctly, the products should be checked against their label requirements.

2 LEGISLATIVE BASIS

2.1 Directive 2001/83/EC*

Directive 2001/83/EC*, is the primary legal instrument for exercising control over the entire chain of distribution of medicinal products within Member States, and also where wholesaling operations cover several Member States simultaneously. This directive is available from the European Medicines Agency website.

Article 80(g) of Directive 2001/83/EC refers to the requirement that wholesalers of medicinal products for human use must comply with the guidelines on Good Distribution Practice of Medicinal Products for Human Use. These guidelines (hereafter referred to as the GDP guidelines) are published separately and form the basis for quality systems for wholesalers.

Reference should also be made to the 'Guide to Wholesaling and Brokering of Medicinal Products for Human Use in Ireland' which is available on the 'Publications and Forms' section at www.hpra.ie.

Compliance with the EU guidelines on GDP is the minimum requirement that a wholesaler must meet in order for a wholesaler's licence to be issued. Compliance with GDP is also a condition on both human and veterinary manufacturer's licences.

2.2 Medicinal Products (Control of Wholesale Distribution) Regulations 2007*

The requirements under Directive 2001/83/EC have been transposed into national legislation by the Medicinal Products (Control of Wholesale Distribution) Regulations 2007 (S.I. No. 538 of 2007)*. The requirements set out in these regulations are discussed in detail in the 'Guide to Wholesaling and Brokering of Medicinal Products for Human Use in Ireland'.

The standard provisions for a wholesaler's authorisation are set out in schedule 2 of S.I. No. 538 of 2007*. Specifically paragraph 5 of Schedule 2 of the Regulations require that wholesaler maintain such staff, installations, premises, equipment and procedures to avoid deterioration of the products that they wholesale.

2.3 European Union Guidelines on Good Distribution Practice of Medicinal Products for Human Use

The EU GDP guidelines are a set of instructions that the wholesaler must comply with, as required by paragraph 13 of Schedule 2 of the regulations.

** as amended*

The EU GDP guidelines contain requirements detailed under the headings: principle, personnel, documentation, premises and equipment, deliveries to customers, returns, recalls, and self-inspections.

The contents of these guidelines are discussed in more detail in the 'Guide to Wholesaling and Brokering of Medicinal Products for Human Use in Ireland'.

3 COLD STORAGE/COLD-CHAIN

3.1 General conditions for all types of cold storage

An increasing number of medicinal products require controlled storage and transportation conditions of between 2°C and 8°C. Such medicinal products must be maintained within the narrow temperature range above freezing point throughout the distribution chain. The temperature conditions under which medicinal products are maintained over this period are referred to as the 'cold-chain' and such conditions must be assured by the manufacturer, shipping agent, wholesaler and pharmacist.

When deciding on the type of cold storage system to be installed the following should be taken into consideration:

- The nature of the products and the volumes/quantities to be stored.
- The level of electronic control of the refrigerator unit, i.e. the ability of the unit to control temperature within specified limits.
- The power back-up facilities for the unit itself and for the temperature monitoring and recording system.
- The condensate from the chiller units should not be collected inside the cold store in an open vessel.
- The internal layout of the cold storage area should ensure that the product is only stored in areas shown by temperature mapping to provide adequate temperature control. Procedures should ensure that product is not stored directly on the floor. It should also be ensured that the storage area is not loaded in such a way as to prevent or restrict airflow and so reduce the cooling ability of the unit. The capacity of the storage area should be sufficient for the purpose.
- The type of temperature monitoring equipment used (e.g. maximum/minimum thermometers (max/min), continuous electronic monitoring, temperature probes, etc.) and their suitability and quantity with respect to the level of product risk. Auto-defrost should be available and the temperature within the unit should not be affected during the defrost cycle.
- Recording probes should be independent of controlling probes.
- Recording sensors/probes are to be placed in locations with the greatest temperature variability as determined by temperature mapping studies; these should also encompass the hot/cold spots within the system.
- The procedures for checking functionality and compliance of the unit with its temperature specifications (i.e. daily checks).

- The temperature records generated and the procedure for their review and approval.
- Recording/monitoring probes should be calibrated regularly (i.e. certified that they are operating correctly and the certification should be traceable to a national standard) to cover the operating range. A minimum of a three-point calibration is preferable and should be carried out on an annual basis.
- The maintenance requirements for the system and potential downtime for maintenance to be conducted.
- The installation of an alarm/alert system, and the procedure for responding to those.

3.2 Small volume operations

As a minimum, the use of a max/min thermometer should be employed as a means of continuous temperature monitoring.

The thermometer(s) should be placed within the load in a location which has been assessed to be the worst case and the temperature should be measured continuously.

The use of a risk assessment should be employed to identify suitable monitoring locations. Temperature mapping should be utilised as part of the risk assessment to identify these locations.

It is important to note, in the case of small volume operations, the implications of storing products in a location which is affected by repeatedly opening and closing the door.

The thermometer(s) should be read and reset daily. Records of the max/min temperatures should be maintained and reviewed independently by the Responsible Person on a monthly basis. A record of this review should be maintained.

Sufficient space should be maintained between the products and the internal surfaces so as to permit adequate air circulation.

If the refrigerator is filled to capacity, the effect on temperature distribution should be investigated. This should include an assessment of this impact in a temperature mapping study.

In the case of high-risk products (e.g. vaccines, insulins, blood products such as Factor VIII), refrigerators should be capable of maintaining the temperature between 2°C and 8°C with the minimum of intervention.

Temperature monitoring devices should be calibrated as described in section 7.

If an alarm is fitted, the functionality of the alarm should be checked periodically as per section 10.

Refrigerators should not be sited in an environment where extremes of temperature may affect their performance. If refrigerators are moved, remapping may be required to assess any impact of the move on the thermal stability of the unit.

If set points of refrigerated systems are changed, remapping should be conducted.

3.3 Large volume operations

For large refrigerators and walk-in cold rooms the internal air temperature distribution should be mapped on installation in the empty and full states. External conditions should also be taken into consideration during the mapping exercise, as extremes of temperature may adversely affect the performance of the refrigeration unit. To enable this, an ambient probe should be located outside of the unit.

For walk-in units, temperature mapping should be repeated if significant changes take place (e.g. repair or replacement of the refrigeration unit or changes to the internal storage layout). In units where a duty/back-up condenser is in place and alterations are made to the running of either unit, remapping is required. This includes changing which unit is the main unit and which is the back-up. If these units are routinely rotated, both units should be included within a mapping study.

These units may be monitored with an electronic continuous temperature-recording device that measures load temperature in one or more locations, depending on the size of the unit. Portable data-loggers that can be downloaded onto a computer may be used instead of a fixed device. As a minimum, the use of max/min thermometers should be employed as a means of continuous temperature monitoring.

Product temperature monitoring may also be used. This involves the use of a temperature probe located within a buffer to simulate the temperature of the products in question. It must be noted that if this method is utilised to continuously monitor the temperature of the product, it must also be used as part of the initial temperature mapping study. The method of temperature monitoring (i.e. product monitoring versus air temperature) must be identical to that utilised in the temperature mapping exercise. It should also be ensured that the size and type of buffer are reflective of the products being stored within the unit to ensure comparability.

Temperature recording probes should have an accuracy of at least +/- 0.5°C.

Records should be checked daily and independently reviewed on a monthly basis by the Responsible Person. Procedures should be in place for prompt notification of any deviations outside specified limits to the Responsible Person. Investigations into deviations outside the limits must be documented.

Products should not be stored in areas shown by temperature mapping to present a risk (e.g. in the airflow from the refrigeration unit). A system should be in place to prevent storage within these areas.

Alarms should be fitted to the unit as described in section 10.

In cases where temperature alarms are fitted and excursions from the acceptable limits are indicated audibly in real-time and personnel notified out of hours, then the frequency of checking the temperature monitoring records may be extended. The rationale for the frequency set should be documented and justified.

Temperature monitoring devices should be calibrated and maintained as described in section 7.

3.4 Freezers

A certain number of products require storage and transportation in a frozen state (e.g. some blood products).

These products will be labelled with specific storage temperature requirements, e.g. 'Store in freezer'. Other products may be labelled with a storage temperature range, e.g. 'Store below -20°C'.

A temperature mapping exercise should be employed as part of a risk assessment to identify the monitoring locations and also the suitability of the unit.

For small volume operations, a continuous temperature monitoring system must be employed. If the freezer is filled to capacity, the effect on temperature distribution should be investigated and documented. These units must be capable of maintaining the required storage temperature such that the maximum and minimum storage temperatures are not exceeded. Max/min temperatures should be checked and recorded daily and independently reviewed on a monthly basis by the Responsible Person. Procedures should be in place for prompt notification of any deviations outside specified limits to the Responsible Person. Investigations into deviations outside the limits must be documented.

For large freezers and walk-in units, the internal air temperature distribution should be mapped on installation in the empty and full states. Temperature mapping should be repeated if significant changes take place (e.g. repair or replacement of the unit or changes to the internal storage layout). External conditions should also be taken into consideration during the mapping exercise, as extremes of temperature may adversely affect the performance of the refrigeration unit. These units should be monitored with an electronic continuous temperature-recording device that measures load temperature in one or more locations, depending on the size of the unit. Portable data loggers that can be downloaded onto a computer may be used instead of a fixed device. Records should be checked daily and independently reviewed on a monthly basis by the Responsible Person. Procedures should be in place for prompt notification of any

deviations outside specified limits to the Responsible Person. Investigations into deviations outside the limits must be documented.

Products should not be stored in areas shown by temperature mapping to present a risk. Sufficient space should be maintained between the products and the internal surfaces so as to permit adequate air circulation.

For walk-in units, temperature mapping should be repeated if significant changes take place (e.g. repair or replacement of the refrigeration unit or changes to the internal storage layout).

Temperature alarms should be fitted to large and walk-in units and those smaller units used to store products at risk. In cases where temperature alarms are fitted and excursions from the acceptable limits are indicated audibly, in real-time, and personnel notified out of hours, then the frequency of checking the temperature monitoring records may be extended. The rationale for the frequency of checking temperature monitoring records should be documented and justified.

All freezer storage units must be capable of maintaining the required storage temperatures for the particular products in all parts of the load and load temperatures should be continuously monitored and recorded daily.

The temperature monitoring devices should be calibrated on an annual basis against a certified, traceable reference standard.

The storage/transportation of products requiring freezing should be such that the product is kept within acceptable storage temperature ranges at all times and that maximum and minimum storage temperatures are not exceeded.

Temperature excursions during storage or transportation should be investigated as described in section 6.

Freezers used for the purposes of freezing ice packs to be used within insulated shipping containers should be subject to the same qualification and control measures as per freezers used for the storage of medicinal products.

3.5 Transportation of cold-chain products

The method and time of transportation, the local seasonal temperatures and the nature, size and temperature control requirements of the load should all be considered when arranging cold-chain distribution.

3.5.1 Small volume transportation

For transport of small volumes of cold-chain goods, insulated containers with ice packs may be used. Products damaged/denatured by freezing must not come in direct contact with ice packs at sub-zero temperatures therefore these containers should have compartments or baffles to separate products from the temperature stabilising materials such as ice packs or eutectic plates. Controls should also be in place to prevent condensation from ice packs from causing damage to products and packaging.

The consignment of cold-chain goods should be clearly labelled with the required storage/transport conditions.

If ice packs are in use, there should be a system in place to control their re-use and a rotation system for ice packs should be in place to ensure that 'unfrozen/warm' ice packs are not used in error.

The control of ice packs should be proceduralised and the time for refreezing of ice packs should be considered and form part of the validation of the cold-chain. If applicable the conditioning time (i.e. time over which ice pack temperature is equilibrated prior to use) should also form part of the validation exercise.

There should be a procedure in place for investigating cases where goods have been transported at temperatures outside of those specified for the products and for implementing corrective actions. Excursions should be investigated as described in section 6.

The transportation of products in insulated containers must be qualified to ensure that the products are protected from extremes of high temperatures and from freezing. The maximum length of time for which the product is maintained within the required temperature range within the insulated container should be determined. This time period must be determined for expected/anticipated extreme conditions, i.e. the extremes of temperature that may be experienced by the insulated container in transit. Consideration should also be given to the seasons of the year and the differences in expected ambient temperatures throughout the year. A different summer and winter configuration for the insulated container may be required. Validations performed on insulated containers should demonstrate that the container can maintain the required temperatures whether the container is full or empty. If it is a requirement that containers are opened and closed throughout deliveries, this should be included in validation studies also. These conditions must also be considered for representatives' samples kept in car boots and goods distributed using postal services or couriers but requiring transportation at low temperatures.

Qualification studies should be performed using the actual conditions to be used for actual product transportation. Therefore, studies performed within environmental chambers are not considered to be reflective of actual conditions. Studies should include sending containers with loggers within to the furthest location to which delivery is proposed.

It should be clear to persons receiving the product that the goods have been received within the validated time limit for the particular type of insulated container. To verify this the time of packing the product into the container should be recorded and not the time of dispatch.

The receiver should place the products in an appropriately refrigerated area immediately upon receipt. It is important to note that products which are transported in insulated containers should be unpacked before storing, as refrigeration upon receipt of small parcels in insulated shippers with ice packs could negatively impact the product contents causing the internal temperatures of the package(s) to drop below the minimum allowable temperature.

3.5.2 Large volume transportation

Larger volumes of cold-chain goods should be shipped in refrigerated transport vehicles, particularly if transit times may be prolonged.

Temperatures within a load of product at risk of freezing should be strictly controlled and monitored with recording probes or individual temperature monitoring devices, giving consideration to the temperature gradient within the load. Calibrated data loggers should be used for this purpose. If single use monitoring devices are used, these should be qualified.

There should be a procedure in place for implementing corrective action in the case of the goods having been transported at temperatures outside of those specified for the products.

The receiver should place the products in an appropriately refrigerated area immediately upon receipt.

Refrigerated vehicles/transportation containers should be validated and monitored if they provide the primary means for environmental control. This includes temperature mapping within the container or transit van to determine hot/cold spots and under 'worst case' conditions, i.e. when the container/van is loaded to capacity, and anticipated extremes in seasonal temperatures in order to take into account worst case scenarios. All operational parameters should be considered during the validation, e.g. door openings, powers sources for refrigeration plant, van breakdowns, etc.

Validation of transportation vehicles is not necessary if the transportation container and the packaging configuration provide the primary means of environmental control for the product and these in turn have been validated.

3.6 Return of cold-chain products

Criteria for accepting returns should be established and there should be mechanisms in place for ensuring that storage conditions are maintained when the product is outside the wholesaler's control.

The HPRA policy is that cold-chain products may only be returned to saleable stock where there is no reasonable possibility that the cold-chain has been compromised. For example, under the following circumstances, the return of product could be considered:

- The batch number of the distributed product is known, and was recorded by the wholesaler.
- The entire process is validated (i.e. delivery to customer, opening of the packaging, examination of the product, returning of the product to the packaging and sealing of the packaging, collection by the courier/transporter, and return to the distribution site refrigerator).

Alternatively, return of cold-chain products could be considered where there is a unique monitoring system attached to the product which would demonstrate whether the product has been stored outside refrigerated conditions.

4 CONTROLLED TEMPERATURE STORAGE/TRANSPORTATION

For the purposes of this document, 'controlled temperature storage' is defined as the storage requirements for products not requiring cold storage or freezing.

Unless otherwise indicated in product literature and labels, medicinal products can be stored under conditions of room temperature without compromising stability or recommended shelf life. The temperature storage indications for these products are, for example, 'Do not store above 25°C', 'Do not refrigerate', 'Do not store above 30°C'.

Controlled room temperature implies a certain degree of control over the temperature of the storage conditions in that extremes of hot and cold temperatures are not encountered.

Temperature mapping should be performed on all storage areas to ensure that all locations are likely to remain within the specified temperature limits over the seasons of the year.

Warehouses should be temperature mapped in the empty and full states to determine the temperature distribution under extremes of external temperature. The mapping exercise should be performed both during summer and winter in order to assess worst-case scenarios, as extremes of temperature may adversely affect the temperature distribution within the warehouse storage area.

Temperature mapping should be repeated after significant modification to the premises, changes in stock layout or changes to the heating system. Due considerations should also be given where the practice of turning off heating systems overnight or over weekends is employed. In general, medicinal products should not be stored next to sun-facing windows, at high levels in poorly insulated stores, at high levels under or near fluorescent lights, or next to heaters. Storage areas beneath skylights should be investigated during mapping studies to ascertain suitability for storage there. Medicinal products should not be stored in areas shown by the temperature mapping to be unsuitable.

A continuous temperature monitoring system is required for the storage of medicinal products. The extent of temperature monitoring necessary for the storage of these products and the locations to be monitored will depend upon the size of the facility and the results obtained from the temperature mapping studies.

The minimum requirement is that the use of a calibrated max/min thermometer be employed. The max/min thermometer(s) should be placed at appropriate strategic locations, identified during temperature mapping studies, throughout the warehouse, and read, recorded and reset daily. Electronic continuous temperature-recording devices that measures load temperature in one or more locations may be employed. Portable data loggers that can be downloaded onto a computer may also be used instead of a fixed device.

The temperature monitoring devices should be calibrated on an annual basis against a certified, traceable reference standard. Calibration certificates should be reviewed and approved by the wholesaler to ensure acceptability.

With the exception of very small stores, the locations for the max/min thermometers should normally include all levels of the facility where medicinal products may be stored. The frequency of reading and recording the temperatures should be increased during periods of exceptionally hot or cold weather. Other areas such as self-contained storage units (e.g. controlled drug storage) should also be included in the temperature mapping and subsequent monitoring programmes.

Records should be checked daily, and independently reviewed and approved on a monthly basis by the Responsible Person. Procedures should be in place for prompt notification of any deviations outside specified limits to the Responsible Person. Investigations into deviations outside the limits must be documented.

The method and time of transportation, the local seasonal temperatures and the nature, size and temperature control requirements of the load should all be considered when arranging distribution of medicinal products.

These conditions must also be considered for representatives' samples kept in car boots and goods distributed using postal services or couriers.

There should be a procedure in place for implementing corrective action in the case of the goods having been transported at temperatures outside of those specified for the products.

5 MEAN KINETIC TEMPERATURE

Mean kinetic temperature (MKT) is defined by the ICH as 'A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.'

The Haynes formula can be used to calculate the MKT. It is higher than the arithmetic mean and takes into account the Arrhenius equation from which Haynes derived his formula. Thus, MKT is the single calculated temperature that stimulates the non-isothermal effects of storage temperature variations.

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

Where:

T_k = MKT in °K
ΔH = Heat of activation/activation energy
R = Universal gas constant (8.3144 X 10^{-3} kJ.Mole^{-1}. °K^{-1})
T = Temperature in °K
n = Total number of equal time periods over which data are collected

The practical application of this equation is less complex than it first appears. For a wide range of pharmaceuticals, ΔH is in the range of 42 – 125 kJ/mol. Because the relationship of reaction rate to activation energy and temperature is exponential, a small change in temperature or activation energy causes a large change in the rate of the reaction. The activation energy and rate of a reaction are related by the equation (Arrhenius):

$$k = Ae^{-Ea/RT}$$

Where:

k = The rate constant
A = Temperature-independent constant (often called the frequency factor)
E_a = Activation energy
R = Universal gas constant
T = Temperature °K

Activation energies are usually determined experimentally by measuring the reaction rate *k* at different temperatures *T,* plotting the logarithm of reaction rate k against 1/*T* on a graph, and determining the slope of the straight line that best fits the points.

MKT is also 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. In other words, as the degradation rates of drugs change with temperature, it is difficult to determine exactly how much a drug may have degraded when its storage temperature is not maintained constant.

As the temperature decreases, the degradation rate decreases and as the temperature increases, the degradation rate increases. MKT is a concept of an integrated time/temperature function as it relates to degradation. It is similar to developing an area-under-the-curve (AUC) function for bioavailability but it relates to time and temperature. As the temperature increases with time, the AUC increases, hence the extent of drug degradation would be greater as the AUC is greater. The opposite would also be true; with a decrease in temperature with time, the AUC decreases and the extent of drug degradation under these conditions would be less.

Hence, the mean kinetic temperature may be considered as an isothermal storage temperature that simulates the non-isothermal effects of storage temperature variation. It is not a simple arithmetic mean but involves exponential and logarithmic relationships.

MKT refers to a reference point, which can be calculated from a series of temperatures. It differs from other means in that higher temperatures are given greater weight in computing the average. This weighting is determined by a geometric transformation, the natural logarithm of the temperature number. Disproportionate weighting of higher temperatures in a temperature series according to the MKT recognises the accelerated rate of thermal degradation of materials at these higher temperatures. MKT accommodates this non-linear effect of temperature.

In order for MKT to be meaningful in anyway, an appropriate number of temperature/time sampling points should be used. MKT may only be applied in situations where temperature control of the storage area is good, but where occasional excursions do occur due to seasonal variation.

MKT may only be applied in cases where the scientific data regarding the thermal stability of the product in question, used to establish the original labelled storage conditions, permits limited excursions between 25°C to 30°C. The MA holder should be consulted as to whether these excursions affect the thermal stability of the products in question and hence whether or not the use of MKT is applicable.

Strict conditions should be applied to the use of MKT, i.e.:
- It is only applicable to storage of products under controlled room temperature conditions (e.g. those labelled ‘Do not store above 25°C’).
- It is not appropriate for use for products requiring controlled low temperature storage.

- It cannot be used to compensate for poor temperature control of storage facilities due to, e.g. poor design of premises or ventilation.
- Excursions outside labelled storage requirements for products should be documented, investigated and reported to the MA holder.
- Actual storage temperatures should not exceed 30°C at any point if MKT is to be applied, i.e. for an MKT of 25°C, excursions between 15°C and 30°C are permitted.

The application of MKT should be detailed in a written procedure. The maximum limit for MKT for a product requiring storage at or below 25°C is 25°C, so in theory this allows for excursions of between 15°C and 30°C. The number of excursions permitted above the labelled maximum temperatures should be limited and consistent with good warehousing and distribution practice.

To summarise, finished medicinal products may vary considerably in their thermal stability. Given this fact, any excursions outside the stated label storage requirements should be investigated and notified to the MA holder. The MA holder should be consulted as to whether excursions outside the labelled storage temperature requirements affect the thermal stability of the products in question and hence whether or not the use of MKT is applicable.

6 MANAGEMENT OF TEMPERATURE EXCURSIONS

A temperature excursion is a deviation from the labelled storage conditions of a product for any duration of time whether during storage or transportation. All excursions should be promptly and thoroughly investigated.

- Temperature excursions should be notified immediately to the Responsible Person.
- Temperature monitoring records should be regularly reviewed and approved to ascertain whether an excursion may have occurred.
- Any products stored within the affected area should be quarantined until the outcome of the investigation is known.
- Investigations performed should be documented including the outcome of investigations.
- The management of temperature excursions should be described within a procedure.
- The manufacturer/marketing authorisation holder should be consulted to ascertain whether any possible product quality impact may result from the excursion.
- If a recall may be required, the HPRA should be notified immediately.
- Excursions within freezers or fridges used for the storage of ice/chill packs for insulated shippers should be investigated with equal thoroughness.
- Corrective actions should be identified and implemented following the investigation to prevent reoccurrence.

7 CALIBRATION OF MEASURING DEVICES

Temperature monitoring probes should be calibrated to ensure that they are operating within the manufacturer's specifications for that probe.

Calibrations of probes should be strictly controlled as follows:

- Probes should be calibrated at least annually against a traceable reference device.
- Probes should not be used after the recommended recalibration date.
- Calibrations should be performed at least three points across the range of temperatures for which the probe will be used (e.g. 0, 15 and 30 °C for ambient warehouse probes; -10, 0, 10 °C for refrigerator probes).
- All calibration certificates should be reviewed and approved by the wholesaler to ensure that the calibration results for the probes are acceptable.
- Calibration certificates should state the method used for the calibration of the probes.
- Calibrations should be conducted on the entire monitoring system (for example, not just a simulated calibration of a receiver box but should encompass the entire system – probes, receiver box, display unit if applicable).
- Should a probe fail calibration then a review should be performed to assess any possible impact on previous readings.
- The calibration of probes should be described within a procedure.
- Calibration certificates should be available for review by an HPRA inspector.
- Auxiliary probes should be in place so that the temperature of relevant storage areas is monitored whilst calibrations are being conducted. If a lower number of probes are in use during calibrations then the locations of these probes should be based on a risk assessment. The use of auxiliary probes should be documented using serial numbers and calibration certificates for these probes should be maintained.

8 WRITTEN PROCEDURES AND RECORDS

Procedures concerning temperature monitoring should include the frequency of monitoring (i.e. daily), location of devices (e.g. map of the area with locations of temperature monitoring devices identified on the map), 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.

All records should be readily retrievable and be in such a form as to make it possible to identify any temperature excursions. All records should be reviewed and the review should be recorded.

9 TRAINING

Appropriate training should be provided for all staff members involved in the storage and 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 their specific responsibilities. Training on relevant items contained within this guidance document should be included in the training program.

There should be a written procedure which describes the training programme and training records should be retained for each employee.

10 MONITORING ALARMS AND ALARM CHECKS

Where possible temperature monitoring systems should have an alarm function installed. This system should immediately notify relevant personnel if a temperature excursion occurs.

Set points for alarms may contain both alert and action limits. The alert limits should be set so as to allow preventive actions to be completed prior to an excursion occurring.

Alarms should be regularly checked for functionality at the designated set points. The performing of this check should be carried out in a manner such that products contained in the unit are not subjected to out-of-specification temperatures. Records of this should be maintained.

Alarms may be local or may alert relevant personnel by phone or email. Provision for an out-of-hours response should be made. Alarm nominees should be trained in the actions which they may take in the event of an alarm situation. These possible actions along with the use of the alarms and set points should be described in a procedure.

Probes should be situated within an appropriate load simulator so that transient rises in temperature (e.g. when the doors are opened during picking) do not trigger alarms.

11 CONTACT DETAILS

For further information contact:
Compliance Department
Health Products Regulatory Authority
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2

Telephone: +353-1-6764971
Fax: +353-1-6764061
Email: compliance@hpra.ie

APPENDIX 1 REFERENCES

1 EU Guidelines on Good Distribution Practice (GDP) of Medicinal Products for Human Use
2 Taylor J, Recommendations on the control and monitoring of storage and transportation temperatures of medicinal products. The Pharmaceutical Journal, 28 July 2001, Volume 267, pages 128-131
3 Health Products Regulatory Authority 'Guide to Wholesaling and Brokering of Medicinal Products for Human Use in Ireland'
4 CPMP Note for guidance on declaration of storage conditions
5 A: In the product information of medicinal products
6 B: For active substances
7 ICH Guideline – Stability testing of new drug substances and products (Q1A(R2))
8 CPMP Note for Guidance on Declaration of Storage Conditions (CPMP/QWP/609/96/Rev1)
9 ICH Guideline – Evaluation for Stability Data – Q1E
10 US Pharmacopoeia
11 Medicinal Products (Control of Wholesale Distribution) Regulations 2007*