



IRISH MEDICINES BOARD

**GUIDE TO CONTROL AND MONITORING OF STORAGE  
AND TRANSPORTATION TEMPERATURE CONDITIONS  
FOR MEDICINAL PRODUCTS AND ACTIVE SUBSTANCES**

**EDITION IND- 003 VERSION 01  
MARCH 2006**

This guide does not purport to be an interpretation of the law and/or regulations relating to cold chain temperature and is for guidance purposes only.

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## 1. INTRODUCTION

The purpose of this document is to provide guidance to medicinal product manufacturers (Human and Veterinary), wholesalers and transporters of human medicinal products in Ireland and manufacturer's 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°
- 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. Indeed, 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 employed 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 thus 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.

For any given time of the year, conditions within the distribution chain can vary markedly. 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**

### **Directive 92/25/EEC**

The initial legislation which introduced the concept of wholesale distribution, European Directive 92/25/EEC, was adopted for the purpose of exercising control over the entire chain of distribution of medicinal products within Member States, and also where wholesaling operations covered several Member States simultaneously. Directive 92/25/EEC is now incorporated into Directive 2001/83/EC on the Community code relating to medicinal products for human use.

Article 6 (g) of directive 92/25/EEC, now 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.

Refer also to the IMB published “Guidance Document on the Wholesaling of Medicinal Products for Human Use in Ireland”.

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.

### **Medical Preparations (Wholesale Licences) Regulations, 1993 – 1996, as ammended**

Directive 92/25/EEC was transposed into Irish legislation under the Medical Preparations (Wholesale Licences) Regulations, 1993 – 1996 (S.I. No. 39 of 1993 and S.I. No. 41 of 1996).

The standard provisions for a wholesaler’s licence (WLs) are set out in Article 7 (2) of the Medical Preparations (Wholesale Licences) Regulations, 1993, as amended. Section (c) requires that a licence holder:

(c) Shall provide and maintain such premises, equipment and staff, and have in operation such arrangements as are necessary to avoid deterioration of the medicinal product to which the licence relates and shall notify the IMB promptly of any material change in such premises, equipment, staff or arrangements.

## **European Union Guidelines on Good Distribution Practice of Medicinal Products for Human Use:**

The following are the requirements of the different sections of the EU Guideline on GDP relevant to storage conditions and maintenance of the storage and transportation temperature requirements.

### Premises & Equipment

- 9 Premises and equipment should be suitable and adequate to ensure proper conservation and distribution of medicinal products. Monitoring devices should be calibrated.

### Receipt

- 10 Medicinal products subject to specific storage measures (e.g. narcotics, products requiring a specific storage temperature) should be immediately identified and stored in accordance with written instructions and with relevant legislative provisions.

### Storage

12. Medicinal products should normally be stored apart from other goods and under the conditions specified by the manufacturer in order to avoid any deterioration by light, moisture or temperature. Temperature should be monitored and recorded periodically. Records of temperature should be reviewed regularly.
13. When specific temperature storage conditions are required, storage areas should be equipped with temperature recorders or other devices that will indicate when the specific temperature range has not been maintained. Control should be adequate to maintain all parts of the relevant storage area within the specified temperature range.

### Deliveries to Customers

20. Medicinal products should be transported in such a way that:
- (d) They are secure and not subjected to unacceptable degrees of heat, cold, light, moisture or other adverse influence, nor to attack by micro-organisms or pests.
21. Medicinal products requiring controlled temperature storage should also be transported by appropriately specialised means.

### Returns

23. Products which have left the care of the wholesaler, should only be returned to saleable stock if:
- (a) The goods are in their original unopened containers and in good condition.
  - (b) It is known that the goods have been stored and handled under proper conditions;
  - (c) The remaining shelf life period is acceptable;
  - (d) They have been examined and assessed by a person authorised to do so. This assessment should take into account the nature of the product, any special storage conditions it requires, and the time elapsed since it was issued. Special attention should be given to products requiring special storage conditions. As necessary advice should be sought from the holder of the marketing authorisation or the Qualified Person (QP) of the manufacturer of the product.

### **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 is referred to as the ‘cold-chain’ and such conditions must be assured by the manufacturer, shipping agent, distributor 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. 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 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.
  
- 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.

### **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 the 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.

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.

In the case of high risk products (e.g. vaccines, insulin's, 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.

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

If an alarm is fitted, the functionality of the alarm should be checked periodically at the upper and lower set points.

Refrigerators should not be sited in an environment where extremes of temperature may affect their performance.

### **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.

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).

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 a max/min thermometer 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 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.

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).

Temperature alarms should be fitted to large and walk-in units and those smaller units used to store products at risk from freezing and suitable limits should be set. 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. Provision for out-of-hours response should be made. These alarms should be tested periodically.

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.

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

### **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  $-20^{\circ}\text{C}$ ".

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

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.

For small volume operations, 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 maximum and minimum storage temperatures are not exceeded.

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.

### **3.5 TRANSPORTATION – 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.

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 the 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. 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 implementing corrective action in the case of the goods having been transported at temperatures outside of those specified for the products.

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. 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.

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.

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.

### **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, then 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. However this is not necessary if a qualified insulated container is used as the primary means of 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.

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 RETURNS – 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 IMB position 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:
- 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 is utilised to imply 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. 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.

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 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.

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

T <sub>k</sub>	=	MKT in °K
ΔH	=	Heat of activation / activation energy
R	=	Universal gas constant (8.3144 X 10 <sup>-3</sup> kJ.Mole <sup>-1</sup> .°K <sup>-1</sup> )
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):

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

k	=	the rate constant
A	=	temperature-independent constant (often called the frequency factor)
E <sub>a</sub>	=	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.

Mean Kinetic Temperature (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 this 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.

Mean kinetic temperature 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.

It is calculated from the average storage temperatures recorded over a time period and a running average calculated from the average of weekly high and low temperatures.

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)
- MKT is not appropriate for use for products requiring controlled low temperature storage.
- MKT cannot be used to compensate for poor temperature control of storage facilities due to e.g. poor design
- Excursions outside labelled storage requirements for products should be documented and 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. 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 in the event the temperature deviates outside the limits. Detailed investigations and the outcome of such investigations into temperature excursions should be documented.

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.

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

If ice-packs are in use, there should be a system in place to control the 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 as well as the conditioning of ice packs prior to use.

Deviations outside specified limits should be notified promptly to the Responsible Person under a defined procedure and investigated.

## **7. 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 his/her specific responsibilities.

## **8. CALIBRATION OF MEASURING DEVICES**

Manual and electronic measuring and recording devices should be calibrated across their range of use, at least annually against a traceable reference device.

Alarms should be checked for functionality at the designated set points.

## 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) *Irish Medicines Board Guidance document on the wholesaling of medicinal products for human use in Ireland*
- (4) *CPMP Note for guidance on declaration of storage conditions:  
A: In the product information of medicinal products  
B: For active substances*
- (5) *ICH Guideline – Stability testing of new drug substances and products (Q1A(R2))*
- (6) *CPMP Note for Guidance on Declaration of Storage Conditions (CPMP/QWP/609/96/Rev1)*
- (7) *ICH Guideline – Evaluation for Stability Data – Q1E*
- (8) *US Pharmacopoeia*