RISK MANAGEMENT of MEDICINES STORED in CLINICAL AREAS: TEMPERATURE CONTROL

Edition 1

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Risk management of Medicines Stored in Clinical Areas: Temperature Control

1. PURPOSE

This document aims to provide guidance to healthcare professionals on managing the risks associated with storage of medicines outside their manufacturers' recommendations within wards and clinical areas, when control of temperature is not reasonably practicable (e.g. in an ambulance or patients' lockers).

It is not intended to replace the principles of controlled temperature storage as defined in Good Distribution Practice.

2. SCOPE

The guidance in this document applies to storage of medicines in wards and clinical areas in NHS Trusts.

It is not applicable to storage of medicines within the pharmacy controlled supply chain. It also does not apply to storage within patients' own homes, although the information within the document may be of some use to community and home healthcare providers.

3. INTRODUCTION

Medicines in the supply chain between the manufacturer and the pharmacy department are routinely stored in suitably controlled environments, in accordance to Good Distribution Practice.

However, once the medicines have left the pharmacy controlled supply chain (e.g. ward, operating theatre, ambulance, outreach service) strict temperature control cannot always be achieved. This is because there are other considerations to be taken into account e.g.:

- Timely access to medicines, for example in emergency care or where patients need access to their own medicines e.g. inhalers, insulin.
- Safe and secure storage to prevent unauthorised access to medicines

Nevertheless, medicines should be stored under conditions which assure the quality of the medicine until the end of administration to the patient. Any decision to store a medicine outside the stated temperature range must be informed by a robust risk management approach to safeguard patient and public health.

This will involve:

- Taking a risk management approach to determine suitable storage arrangements depending on patients' needs, the type and range of medicines stored, the length of time the medicines will be stored, cost of potential temperature controls, and local environmental factors.
- Temperature monitoring of the medicines storage facilities (whether temperature controlled or not) to give assurance that medicines are safely stored.(Appendix 6)
- Ensuring any risk management measures (e.g. strict stock rotation; shelf life reduction) are properly implemented, monitored and reviewed
- Defining actions to be taken in the event of temperature excursions outside the range specified for the medicines being stored.

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4. RISK BASED APPROACH TO STORAGE OF MEDICINES IN CLINICAL AREAS

This approach takes a patient-centred approach which balances the following needs:

- to have medicines readily available for patients
- to store medicines safely and securely
- to ensure the quality of the medicines is assured

Frequently, healthcare professionals are faced with the challenge of delivering these sometimes conflicting requirements. When all three elements cannot be fully addressed, a benefit/risk management approach will need to be taken to optimise patient outcomes.

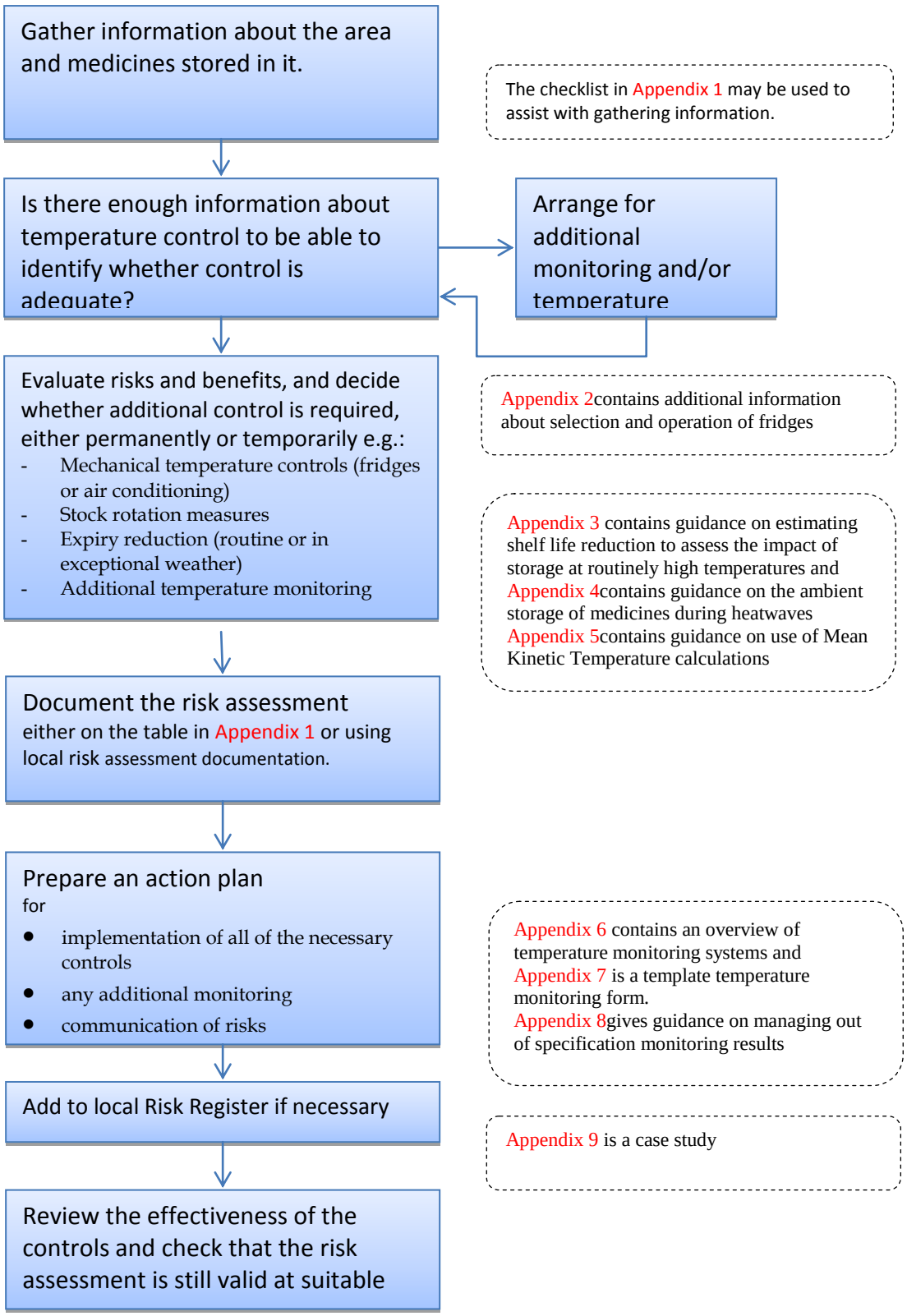
It is not the intention of this guidance to consider every possible scenario, but to advise a risk management approach and to suggest some risk factors to be considered. It should also be noted that storage of a medicine outside of its stated conditions is outside the medicine's licence and would require review under local clinical governance arrangements.

Each circumstance should be assessed individually to determine the appropriate storage and monitoring requirements, and where appropriate to plan contingency arrangements. Assessments could be made for individual medicines or groups of medicines with similar storage needs, or for whole storage areas, depending on the situation.

Assessments should be documented, steps should be taken to control risks and the assessment should be reviewed at intervals to ensure that it is still valid and that risk controls are still effective

The flow-chart overleaf describes the approach that may be taken to assess and manage the risks for a whole clinical area (e.g. hospital ward).

Risk management of storage of medicines in clinical areas – Process



The remainder of this guidance is a series of appendices which either assist with the risk assessment process or provide additional information and tools for controlling the risks associated with storage of medicines in clinical areas:

Appendix 1: Risk identification checklist and risk assessment record

This can be used for information gathering and to assign a RAG rating to risks that have been identified. Other local risk identification and assessment tools could be used if preferred.

Appendix 2: Pharmacy refrigerators

A model purchasing specification, and some “handy hints” about use of refrigerators.

Appendix 3: Q10 calculations

A calculation to be used to determine shelf life reduction when medicines will be stored at higher temperatures than stated on their packaging.

Appendix 4: Guidance on shelf life reduction in the event of a heatwave

Using the Q10 calculation during heatwaves (previously issued by QC North West as stand-alone document in July 2014)

Appendix 5: Mean Kinetic Temperature

Use of Mean Kinetic Temperature calculations in areas where temperatures fluctuate above the upper limit.

Appendix 6: Temperature monitoring

Description of methods of temperature monitoring.

Appendix 7: Template temperature monitoring form

An example refrigerator monitoring record form to be adapted for local use.

Appendix 8: Guidance on managing out of specification results

Guidance about what steps should be taken if temperatures are out of limit, and where to find information to enable an impact assessment to be made.

Appendix 9: Case study

Case study from Newcastle upon Tyne NHS Foundation Trust: How we can determine if Medicines Stored in Ambient Clinical Areas are Correctly Temperature Controlled

REFERENCES

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The safe and secure handling of medicines: A team approach (Royal Pharmaceutical Society) 2005
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http://www.mhra.gov.uk/home/groups/comms-ic/documents/publication/con007569.pdf

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Version 3	
Version 4	

APPENDIX 1: TEMPERATURE CONTROL OF MEDICINES IN CLINICAL AREAS RISK IDENTIFICATION CHECKLIST AND RISK ASSESSMENT RECORD.

Question	Results and observations	Explanatory notes
Information about the clinical area		
Ambient storage areas		
Where in the clinical area are medicines being stored? Locked cupboards, patients lockers etc		Describe how and where all medicines are stored in the clinical area.
How well is the temperature controlled in each storage areae.g. is there air conditioning or chilling, or other means of protection from extremes of temperature.		Storage areas without air conditioning may be protected to a greater or lesser extent from fluctuations of external temperature because of their location or design e.g. insulation, natural ventilation, exposure to direct sunlight; heating/frost protection for cold weather. Temperature control may have been installed for comfort reasons e.g. in neonatal wards the temperature is controlled to between 28 and 32^{O}C, which may be too warm for medicines. The effectiveness of temperature control may vary e.g. there may be local thermostats or it may be centrally set with little ability to change the set point locally.
What temperature monitoring system is in place?		Temperature monitoring systems may be simple max/min thermometers with or without continuous dataloggers, or a continuous remotely monitored system. Remotely monitored systems increase the likelihood of speedy detection of excursions and timely remedial action. Temperature monitoring systems need to be suitable for the location being monitored (see Appendix 6). This includes not only the equipment used for monitoring, but the systems in place to check that the monitoring results are within limits.
What are the frequency and duration of temperature excursions in the area? If there are brief or small excursions, is the mean kinetic temperature known?		Occasional brief excursions to higher temperatures than the stated range may not present any risk to the medicines. The Mean Kinetic Temperature (MKT) can be calculated from multiple individual temperature recordings made by dataloggers or automated monitoring systems: if the

Question	Results and observations	Explanatory notes
		maximum temperature reached is below 40^{O}C and the MKT is below the upper temperature limit for the medicine there is no risk to the medicine. MKT calculations can only be used for higher temperatures: medicines which are made unfit for purpose by storage at low temperatures may be affected by any brief excursion. Max/min thermometer readings cannot be used to make accurate MKT calculations. (see appendix 5)
Has any temperature mapping been done? If so, what are the results?		Temperature mapping should be used in all storage areas to determine hot and cold spots. For uncontrolled areas this should be repeated during extremes of cold and hot weather to ensure the information is accurate (e.g. in winter areas near the window may be particularly cold, but if south facing it may be the hottest spot in the summer).
Refrigerators		
Are refrigerators of pharmacy specification?		The temperature is likely to be variable within domestic refrigerators, and parts of the storage area may routinely drop below freezing. This may be because there is no air distribution fan, or it may be a design feature to store different foods under different conditions (e.g. in door, in salad drawer). Cold chain medicines should always be stored in pharmacy specification refrigerators. (see Appendix 2)
Are refrigerators being used and maintained in such a way as to ensure the internal temperature is within specification throughout the storage chamber?		Temperature variation within a fridge will not be detected by a single point monitoring system, so it is essential to ensure fridges are stocked carefully to allow air circulation, and are properly maintained and cleaned to ensure that they function correctly. (See appendix 2)
What temperature monitoring system is in place?		Temperature monitoring systems may be simple max/min thermometers with or without continuous dataloggers, or a continuous remotely monitored system. Remotely monitored systems increase the likelihood of speedy detection of excursions and timely remedial action.

Question	Results and observations	Explanatory notes
		Temperature monitoring systems need to be suitable for the location being monitored (see Appendix 6). This includes not only the equipment used for monitoring, but the systems in place to check that the monitoring results are within limits. A recording system should be in place: this could be a fully automated system with results fed to a computer program, or a method of manual reading and recording of temperatures. (see Appendix 7) Whichever system is in use, there should be clear lines of responsibility for making the checks and acting upon the findings if necessary.
General		
Is there a robust means of managing out of specification results?		It is essential that there is a system for responding to out of limit temperatures. This will include investigating to see whether a simple action could address the problem, taking action to protect the stock and assessing the impact on the medicines. Guidance on managing out of limit temperatures is in Appendix 8. If any temperature readings have been out of specification, check whether the action taken was appropriate and whether the decisions have been documented.
Are there any contingency options if there was a loss of temperature control e.g. moving stock temporarily into a suitable area		Any contingency option also needs to consider capacity and access, and also safe and secure storage of medicines.
How long is likely to elapse between the excursion taking place and remedial action being taken		In some instances actions to restore the correct temperature or to move medicines to another location are likely to be delayed e.g. in a clinic that is only staffed for a small proportion of the week, more robust temperature control and monitoring arrangements may be required than for an area that is constantly occupied.
Information about the medicines		
What medicines are being stored in the clinical area?		Is inventory controlled (e.g. stock list) or variable (e.g. patients' own medicines)

Question	Results and observations	Explanatory notes
What are the storage requirements of the medicines?		Some medicines do not have any special storage requirements, or may have an upper limit of 30^{O}C, and so are much less at risk than those with lower temperature storage requirements or those that must not be frozen.
What shelf lives are assigned to the medicines?		Medicines with long shelf lives are less likely to be adversely affected by brief excursions above the stated range than medicines with short shelf lives.
What effect is out of range storage likely to have on the medicine?		Storage out of range will have different effects on different medicines, for example: • at higher temperatures the shelf life may be reduced, but the medicine may still be fit for use if arrangements are made to reduce its expiry date. • the shelf life may be reduced so much that the medicine becomes not fit for use at all • at lower temperatures precipitation of solutions may occur, which may render them not fit for use • if frozen, some medicines (e.g. biologicals) or their containers (e.g. syringes) may be irreversibly damaged and become unfit for use immediately. • Solid dose forms (e.g. tablets, capsules) are likely to be more stable than liquids • Medicines that have been heat sterilised will be stable at high temperatures Information about the effect on individual medicines stored outside their stated range may be available to assist with the risk assessment. e.g. • from the manufacturer, from their own stability studies • from the UKMi network NB. Shelf life reductions can be estimated by use of the a Q10 calculations (see Appendix 3).

Question	Results and observations	Explanatory notes
How long will the medicine be stored in the clinical area? e.g. medicines dispensed for individual patients may be present for only a few days or weeks.		It may be acceptable to store medicines at higher temperatures than the stated range for only a short time (relative to their assigned shelf life) before use if the effect of the higher temperature is taken into account. The reduction in shelf life can be calculated by using a Q10 estimate (See appendix 3) if • the remaining shelf life of the medicine • its upper storage temperature • the length of time for which it will be stored at the higher temperature are known. Organisational controls will need to be put into place to ensure that the reduced shelf life is adhered to e.g. by labelling, or by robust stock rotation. Q10 estimations can only be used for higher temperatures: medicines which are made unfit for purpose by storage at low temperatures may be affected by any brief excursion.
What is the likely consequence of loss of the medicines		Where there are high value medicines or medicines that are difficult to replace without causing treatment delays, the greater the need to have good temperature control, and robust monitoring systems to enable remedial action to be taken quickly.
Other:		

	Initial Risk Assessment				Risk Mitigation Strategy	Residual Risk		
Risk	**Likelihood (Score 1-5*)**	**Consequence (Score 1-5*)**	**Overall Risk Rating (L x C)**	**Comments**		**Likelihood (Score 1-5*)**	**Consequence (Score 1-5*)**	**Overall Risk Rating (L x C)**
Ambient storage								
There is a risk that medicines in this area will be stored at temperatures which will reduce their shelf life s.								
Refrigerated storage								
There is a risk that refrigerated items may be stored at high temperatures which will reduce their shelf lives.								
There is a risk that medicines which must not be frozen will be stored below $2^{O}C$.								
Operational								
There is a risk that temperature excursions will not be detected.								
There is a risk that temperature excursions will not be addressed in time to prevent patient harm and/or loss of stock.								
Other								

*Likelihood and consequence scores should be assigned according to local Trust risk matrices or the NPSA risk matrix
http://www.npsa.nhs.uk/nrls/improvingpatientsafety/patient-safety-tools-and-guidance/risk-assessment-guides/risk-matrix-for-risk-managers/

APPENDIX 2. MEDICINES REFRIGERATORS

1. Specification

- constructed of impervious, cleanable materials both internally and externally;
- single cooler panel without a freezer box, salad drawer or door shelves.
- maintains the temperature between 2ºC and 8ºC;
- automatic defrost;
- grille-type shelving;
- integral air circulating fan;
- child resistant closure and/or lock with removable key

Optional features:

- permanent integral external display of current fridge temperature
- audible or visible alarm when temperature is out of range;
- audible or visible “door open” alarm

2. Care and use of medicines refrigerators

The refrigerator should be sited in a suitable place in accordance with the manufacturer’s installation instructions. Arrangements should be in place for electrical safety testing and refrigerator maintenance according to the manufacturer’s instructions. Refrigerator feet should be adjusted so that the door will close rather than remain standing open if left accidentally ajar.

Its correct functioning should be established before loading, and temperature monitoring equipment installed if necessary. This may involve temperature mapping. See Appendix 6.

Stock should be loaded so that air can circulate and should not be pushed up against the back panel or the fan housing. Stock should be positioned to ensure the shortest dated medicines are at the front.

The use of polystyrene or other insulating boxes to store medicines within the fridge may result in uneven temperatures throughout the load, so they should not be used unless they are an integral part of the packaging of individual medicines.

Refrigerators should be kept clean both inside and out, including removal of dust build-up on the rear panel. They should be inspected regularly for ice build-up which is likely to indicate a fault, and damage to door seals which will result in the fan and compressor being overworked.

Medicines refrigerators should not be used to store food.

APPENDIX 3 – Q10 CALCULATIONS

It is possible to estimate a reduction in shelf life by making a Q10 calculation provided the manufacturer's shelf life and the length of time at a specified temperature is known.

Q10 is the factor by which the rate of a chemical reaction increases with every $10^{O}C$ increase in temperature. The value is 2 or 3 for most chemical reactions, but to give a "worst case" result, a Q10 of 4 should be used.

Q10 calculations can be used in two ways:

1. **To reduce the expiry of a medicine** that will be stored at a known higher temperature than stated on its packaging e.g. medicines to be stored for a few days or weeks in patient's lockers on a warm ward.

   The formula for calculating a reduced expiry is:

$$S_{(T2)} = \frac{S_{(T1)}}{Q10^{(T2-T1/10)}}$$

Where

T1 = max. storage temperature from manufacturer
T2 = actual storage temperature
S(T1) = expiry at T1
S(T2) = reduced expiry
Q10 = reaction rate

Worked examples:

Medicine with 2 years expiry remaining and storage instructions "Store below $25^{O}C$" to be stored at $30^{O}C$

$$S_{(T2)} = \frac{24}{4^{(30-25/10)}} = 12$$

therefore new shelf life is 12 months

Medicine with 1 year expiry remaining and storage instructions "Store below $25^{O}C$" to be stored at $35^{O}C$

$$S_{(T2)} = \frac{12}{4^{(35-25/10)}} = 3$$

therefore new shelf life is 3 months

2. To assess the impact of an unexpected temperature excursion.

Using a Q10 of 4, the rates of degradation for different temperature increases are:

Incremental Temperature Increase	Increased Rate of Degradation
5^{O}C	2
10 ^{O}C	4
15 ^{O}C	8
20 ^{O}C	16
25 ^{O}C	32

So, if a medicine that should be stored in the fridge (avg. 5^{O}C) is stored at 20^{O}C for 24 hours the incremental increase is 15^{O}C. It degrades at 8 times the rate of the refrigerated product during those 24 hours, which therefore reduces the shelf life by 8 x 24 = 192 hours = 8 days.

It can therefore be seen that there would be a small impact on a product which has a 6 month expiry; conversely, an item with only 7 days' expiry would no longer be fit for use.

Worked example:

Ambient Medicine stored at 30 ^{O}C for 1 month and then returned to <25 ^{O}C

Original shelf life: 24 months at 25 ^{O}C.
Medicine stored at 30 ^{O}C for 1 month

Incremental increase in temperature = 5 ^{O}C, therefore degradation increased 2 fold.

Therefore reduction in shelf life = 2 x 1 = **2 months**

New shelf life is 24 - 2 = **22 months**.

APPENDIX 4: GUIDANCE FOR REDUCING THE SHELF LIFE OF MEDICINES IN THE EVENT OF A HEAT WAVE (FIRST ISSUED JULY 2014)

Scope

This guidance is provided to assist North West NHS Trusts in taking a risk based approach to assessing the impact of short periods of hot weather on medicines stored at room temperature (below 25^{O}C). This guidance should be used as part of a risk management strategy to ensure a robust supply of medicines that are safe for patients to use during heatwaves.

Introduction

Medicines specify the required storage temperature on their packaging or labelling and in their SmPC. For ambient storage medicines it is usually stated as a maximum of 25^{O}C or 30^{O}C. In some instances there are no special storage requirements. This may be stated on the packaging, or may only be stated on the pack leaflet or SmPC.

All medicines in this category are relatively robust and are usually allocated a long shelf life (typically 2 years): medicines that are susceptible to degradation by high ambient temperatures over a relatively short period will have more stringent requirements e.g. store in a refrigerator or a cool room, and generally have shorter shelf lives.

However, this method will not be accepted by the MHRA under Good Distribution Practice (GDP), so can only be applied as part of a risk based approach for medicines stored in clinical areas. Full GDP requirements will need to be upheld in the controlled supply chain.

The means of managing reduction in shelf life will need to be determined locally. This could involve labelling or other means of strict stock control to ensure affected packs are used before their revised expiry dates.

Estimating the impact in terms of reduction in shelf life

In the event of medicines being stored at higher temperatures than the range stated on their packaging it is possible to estimate the reduction in shelf life using a Q10 calculation.

Q10 is the factor by which the rate of a chemical reaction increases with every 10^{O}C increase in temperature. The value of Q10 is 2 or 3 for most chemical reactions, but to give a “worst case” result, a Q10 of 4 should be used. The method of calculation of Q10 is given in the supplementary notes to this guidance for reference.

If a Q10 of 4 (i.e. a four-fold rate increase for every 10^{O}C) is assumed, the following table gives the increased rate of degradation for a medicine with requirement to store at 25^{O}C or below as defined in the SmPC.

Ambient temperature	Incremental Temperature Increase	Rate of Degradation increased by factor of:
30 ^{O}C	5 ^{O}C	2
35 ^{O}C	10 ^{O}C	4
40 ^{O}C	15 ^{O}C	8

Worked example

Scenario:

- Medicine with requirement to store at 25^{O}C or below as defined in the SmPC
- Heat wave for 2 weeks with temperature reaching 35^{O}C
- Medicine stored at 25^{O}C or below before and after heat wave

Shelf life reduction estimation:

- There has been a temperature increase of 10^{O}C for period of 2 weeks
- Therefore the rate of degradation increased by a factor of 4 during those 2 weeks (from table above).
- Therefore 2 weeks' storage at 35^{O}C is equivalent to 8 weeks at 25^{O}C
- Therefore the shelf life reduction required = **original expiry date on pack minus 8 weeks**.

Rule of Thumb:

Using the principles above, a general worst case "rule of thumb" can be estimated:

Storage range in SmPC	**Temperature reached**	**Length of time at high temperature temperature**	**Reduce the expiry on the pack by**
25^{O}C or below	25-30^{O}C	24 hours	2 days
	25-30^{O}C	1 week	2 weeks
	30-35^{O}C	24 hours	4 days
	30-35^{O}C	1 week	4 weeks
	35-40^{O}C	24 hours	8 days
	35-40^{O}C	1 week	8 weeks
30^{O}C or below	30-35^{O}C	24 hours	2 days
	30-35^{O}C	1 week	2 weeks
	35-40^{O}C	24 hours	4 days
	35-40^{O}C	1 week	4 weeks

Limitations & Assumptions

The method described is based on the assumption that the reaction kinetics for the degradation does not change with temperature changes. This can be considered valid for small changes in temperature but users should be wary of applying this method to temperatures above 40^{O}C.

This extrapolation does not take into account humidity, so be wary of applying this to medicines that have been removed from their primary packaging.

References

Chemical Stability of Pharmaceuticals, A handbook for Pharmacists. Connors, Amidon & Stella.2nd edition. Wiley-interscience. ISBN 0-471-87955-X

Supplementary notes:

Methodology

This guidance is based on Q10 method for Shelf life estimation (Simonelli & Dresback). Q10 is the factor by which the rate constant increases for a 10ºC temperature increase.

It is the ratio of two different reaction rate constants. Commonly used Q values of 2, 3 & 4 relate to the energy of activation of reaction for temperature for room temperature (25°C). For an arbitrary temperature change (ΔT), from this relationship, an increase in temperature will decrease the shelf life and a decrease in temperature will increase shelf life.

$$Q_{10} = \frac{K_{(T+10)}}{K_T}$$

$$\frac{K_2}{K_1} = \exp\left[\frac{-E_a}{R}\left(\frac{1}{T_2} - \frac{1}{T}\right)\right]$$

$$Q_{10} = \exp\left[\frac{-E_a}{R}\left(\frac{1}{(T+10)} - \frac{1}{T}\right)\right]$$

$$Q_A = \exp\left[\frac{-E_a}{R}\left(\frac{\Delta T}{(T+\Delta T)(T)}\right)\right]$$

$$Q_A = \frac{K_{(T+10)}}{K_T} = Q_{10}^{(\Delta T/10)}$$

Research has demonstrated that the Activation energy (Ea) of chemical decomposition reactions usually falls in the range 12 to 24 Kcal/mol, with a typical value of 19 to 20 Kcal/mol.

A Q10 of 2 provides a conservative estimate of the increased degradation rate, a Q10 of 3 is the most common, and a Q10 of 4 is the worst-case scenario.

Practical application of Q10 methodology to a heat wave situation

A risk based approach would consider the worst case scenario for drug degradation as typically a number of medicines are likely to be affected. The activation energy for the most temperature sensitive medicines would be the top end of the range i.e. 24.5. This would equate to a Q10 of 4 i.e. a four-fold increase in degradation for every rise of 10°C.

APPENDIX 5 - USE OF MEAN KINETIC TEMPERATURE (MKT)

The MKT is a single temperature value, calculated from a series of fluctuating individual temperature measurements, which can be used to identify the overall thermal challenge presented to medicines stored within the area for the period during which the measurements were made. If the MKT remains at or below the upper temperature limit for any given medicine, even though there may be excursions above the upper limit, the stability of the medicine will be unaffected.

Continuous temperature monitoring e.g. using a data logger or continuous "real time" monitoring is required to ensure the calculated MKT is accurate. It cannot be calculated from max/min thermometer readings.

MKT can be calculated manually (see below), using computer software, or some temperature monitoring systems have this functionality inbuilt.

NB:

1. MKT is *not* the same as the mean temperature of a series of readings.

2. It should not be used routinely to compensate for poor storage conditions, but may be of use in areas which are known to experience occasional excursions outside the required temperature

Ref: http://www.mhra.gov.uk/home/groups/comms-ic/documents/publication/con007569.pdf

The formula used to calculate a MKT is:

$$T_K = \frac{\frac{\Delta H}{R}}{-\ln\left(\frac{t_1 e^{\left(\frac{-\Delta H}{RT_1}\right)} + t_2 e^{\left(\frac{-\Delta H}{RT_2}\right)} + \cdots + t_n e^{\left(\frac{-\Delta H}{RT_n}\right)}}{t_1 + t_2 + \cdots + t_n}\right)}$$

Where:

T_K is the mean kinetic temperature in kelvins

ΔH is the activation energy (typically within 60–100 kJ·mol^{-1} for solids or liquids)

R is the gas constant

T_1 to T_n are the temperatures at each of the sample points in kelvins

t_1 to t_n are time intervals at each of the sample points

When the temperature readings are taken at the same interval (i.e., $t_1 = t_2 = \ldots = t_n$), the above equation is reduced to:

$$T_K = \frac{\frac{\Delta H}{R}}{-\ln\left(\frac{e^{\left(\frac{-\Delta H}{RT_1}\right)} + e^{\left(\frac{-\Delta H}{RT_2}\right)} + \cdots + e^{\left(\frac{-\Delta H}{RT_n}\right)}}{n}\right)}$$

Where:

n is the number of temperature sample points

APPENDIX 6: TEMPERATURE MONITORING

1. Routine monitoring

All medicines storage areas should be routinely monitored. In many cases the use of a maximum/minimum thermometer will be sufficient, but in some cases continuous monitoring will be indicated by the risk assessment because this allows the duration of temperature excursions to be seen and, if linked to an alarm system, allows early intervention.

Unless the recordings are made automatically by the monitoring system, records must be kept manually. All monitoring systems should be maintained and calibrated according to the manufacturer's instructions.

Some temperature monitoring systems are described below:

1.1. Digital max/min thermometer for daily manual record

Use of a maximum/minimum thermometer gives assurance that there have been no excursions out of range, but cannot give any information about how long the temperature has been out of range.

These are normally a small box with a digital display giving the current temperature, and a scroll button that displays the "current", "maximum" and "minimum" readings. Some thermometers display all the readings simultaneously. Thermometers with "indoor" and "outdoor" readings should be used with caution as the displays can be confusing.

The readings should be taken at least every day and the thermometer re-set after the reading has been taken. The thermometer must also be reset after a temperature excursion that has returned to normal otherwise the thermometer will continue to display the out of limit reading which could cause unnecessary concern.

- *Ambient measurements*

  The thermometer should generally be placed in a worst case location as identified by temperature mapping or by the risk assessment.

- *Refrigerator measurements*

  Thermometers for measuring fridge temperatures have an additional probe and cable which allows the probe to be positioned in the fridge while the box remains outside the fridge. The probe may be inserted into a bottle of water of approximately the dimensions of the smallest medicine container. This will buffer the probe from very brief changes in air temperature in the fridge e.g. when the door has been opened.

Some fridges have integral max/min displays. The panel used for reading the temperatures is often the same control panel used to set the fridge operating temperature, so it is important not to accidentally alter the set point when taking readings.

1.2. Continuous real-time temperature monitoring

Continuous real-time monitoring is an expensive option, but may be of benefit where there is high value stock. Probes communicate with a base station that records the temperatures at intervals. These are usually linked to a computerised facility monitoring system that is able to raise alerts as soon as a limit is exceeded.

As with manual systems, the probes need to be situated carefully. The results should be examined at frequent intervals e.g. daily or weekly so that any trends can be identified before any limits are exceeded.

1.3. Data loggers

Data loggers are used to make continuous readings but there is usually no display that can be read. Results are obtained by periodic downloading onto a computer. They are generally used for temperature mapping (see below) but can also be kept in an area where max/min thermometers are in use and then downloaded in the event of an out of limit result to find out the length of the excursion.

2. Temperature mapping

Temperature mapping exercises determine the temperature patterns throughout the storage area or refrigerator by placing several dataloggers throughout the area to be studied. They may be left for 24 hours for a refrigerator or several days in an ambient area where variations across a working week need to be established. This will show any cooler or warmer spots so particularly sensitive medicines can be placed in the most favourable location, and thermometers used for routine monitoring may be placed in “worst case” positions.

Mapping may also be performed seasonally to determine the effects of very cold and very hot weather on the storage areas.

APPENDIX 7: EXAMPLE REFRIGERATOR TEMPERATURE RECORD FORM

Ward/area _____ Fridge ref: _____ Month_____ Year _____

Date	Minimum Should be more than $2^{O}C$	Current Should be between $2^{O}C$ and $8^{O}C$	Maximum Should be less than $8^{O}C$	Readings OK?
1				Yes / No
2				Yes / No
3				Yes / No
4				Yes / No
5				Yes / No
6				Yes / No
7				Yes / No
8				Yes / No
9				Yes / No
10				Yes / No
11				Yes / No
12				Yes / No
13				Yes / No
14				Yes / No
15				Yes / No
16				Yes / No
17				Yes / No
18				Yes / No
19				Yes / No
20				Yes / No
21				Yes / No
22				Yes / No
23				Yes / No
24				Yes / No
25				Yes / No
26				Yes / No
27				Yes / No
28				Yes / No
29				Yes / No
30				Yes / No
31				Yes / No

Re-set the thermometer after every reading is taken.

Out of limit results should be reported to: [insert details]

APPENDIX 8: MANAGING OUT OF LIMIT TEMPERATURE READINGS

If there is an out of limit reading this should be investigated and remedial action taken. There should be clear lines of responsibility for checking temperatures, recording the monitoring results, reporting out of limit results, investigating them and for ensuring that an assessment of the affected medicines is made before there is a decision to continue using them.

Key points to consider include:

1. Take immediate action

Fridges:

- Is there an obvious cause that can be remedied? For example:
  - has the power been accidentally turned off?
  - is the fridge door open?
  - does it contain ice build up?
  - has the thermometer or probe been positioned incorrectly or is it damaged?
- Is there is a need to segregate and quarantine the affected medicines pending a risk assessment e.g. if vaccines may have been frozen or if the contents may have exceeded $8^{O}C$ for more than half an hour where highly temperature sensitive medicines are stored.
- If there is no obvious cause, take steps to protect the medicines e.g.
  - keep fridge door closed to insulate the products from the ambient area as much as possible
  - take steps to move the stock into another fridge

Ambient storage areas:

- Is there an obvious cause that can be remedied? For example, has the thermometer or probe been positioned incorrectly or is it damaged?
- Is there is a need to segregate and quarantine the affected medicines e.g. if the temperature has exceeded the upper limit by more than $5^{O}C$, or for more than a day.

- If there is no obvious cause, take steps to protect the medicines e.g.
  - If too warm move stock to cooler areas e.g. on lower shelves, out of sunlight and away from heat-generating equipment
  - if too cold, move stock that should be stored above 15^{O}C to higher shelves and away from windows and outside walls
  - take steps to move the stock to another suitable secure area

2. Report the incident

In all cases, ensure the out of limit result is reported to the appropriate person within the clinical area.

3. Assess the risks

Assess the impact of the temperature excursion on the medicines. If further advice is needed this can be obtained from your Regional Quality Assurance or Medicines Information service.

UKMi have also developed a “fridge enquiries” guideline which may be of use to Trusts
http://www.ukmi.nhs.uk/filestore/ukmiacg/Fridgeenquiriesguidelinegeneric.doc

Conclusions may include but are not limited to

- Quarantine product pending further investigation (e.g. contact the manufacturer.)
- No temperature excursion occurred e.g. faulty temperature monitor.
- Temperature excursion occurred but there will be no impact on the product (e.g. if the Mean Kinetic Temperature is below the upper limit)
- Minor temperature excursion which reduces the expiry of the product: healthcare professionals asked to clearly mark the container(s) and use first.
- Some or all of the medicine is unfit for use: documents steps taken to ensure healthcare professionals do not use unfit medicines.

APPENDIX 9: A CASE STUDY FROM NEWCASTLE UPON TYNE NHS FOUNDATION TRUST: HOW WE CAN DETERMINE IF MEDICINES STORED IN AMBIENT CLINICAL AREAS ARE CORRECTLY TEMPERATURE CONTROLLED

Step 1 – We gathered information about the ambient medicines storage areas within the clinical areas throughout the Trust

We contacted the Estates department to determine the method of temperature control and monitoring for medicinal storage areas throughout the Trust. It was identified that no ambient temperature readings were recorded either centrally or locally by each clinical area. There was no mechanism to reduce the temperature on wards should it increase to greater than 25°C.

A variety of medicines are stored in ambient clinical areas including Trust stock, patients own medicines and medicines stored out with their original packaging e.g. Medi-dose containers.

Step 2 – We reviewed this information

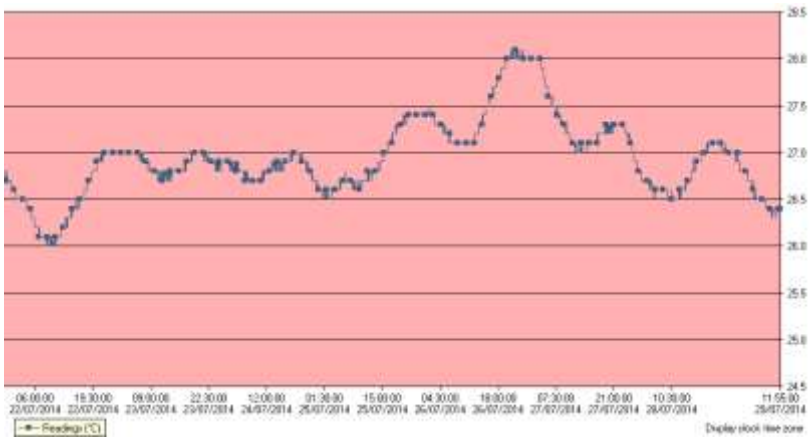
The information gathered was insufficient to assure ambient temperature control of medicines throughout the Trust. We decided that additional monitoring / mapping had to take place to acquire sufficient information.

Step 3 – We performed additional monitoring / mapping

We temperature mapped ambient medicine storage areas throughout the Trust during the winter months to identify base line readings. Continuous temperature monitoring over a 1 week period was undertaken on all intensive care units and a selection of general wards (multiple wards from different wings). The Special Care Baby Unit (SCBU) was the only clinical area identified to routinely exceed 25°C.

We repeated the temperature mapping exercise in the summer months within the same clinical areas (excluding SCBU). We also mapped inside individual storage areas which were associated with the highest environmental temperatures to identify the worst case e.g. highest temperature within the medicines storage cupboard.

- Excursions > 25°C were experienced during periods of hot weather, some clinical areas were associated with higher temperatures and a greater number of excursions than others. Clinical areas which were located in close proximity to one another showed similar results.
- High temperatures experienced during the day (> 25°C) were known to continue overnight in some clinical areas (see graph 1 below). More data analysis is required to determine if e.g. metal storage cupboards are more likely to retain heat.
- The internal medicines storage area was approximately 1-2°C greater than the external environmental temperature (once the external temperature exceeded 25°C).



Graph 1: Continuous temperature records from a general ward in July 2014.

Note: The maximum temperature recorded in the metal storage cupboard was 28.1°C on the 26th of July, the external maximum temperature recorded was 27°C.

Pharmacy areas (stores and dispensaries) are temperature mapped on an annual basis and their temperature is maintained well below 25°C all year round.

Step 4 – We evaluated the risks and benefits and then decided if additional controls were required

We decided that SCBU was the only area associated with a continuous risk of the medicines being exposed to high temperatures. We highlighted this risk to senior directorate management and assigned robust actions to mitigate the risk identified. SCBU required permanent additional controls to assure medicines were being stored at appropriately. An office in this area is to be reconfigured to provide an alternative medicines storage area. During the reconfiguration process an air conditioning unit will be installed to control the temperature.

We decided that temporary controls were to be implemented in all other areas as there is a smaller risk of the medicine being stored out with their SmPC.

Step 5 – We prepared an action plan for the implementation of temporary controls to manage transient temperature excursions

We grouped clinical areas according to the similarity of results obtained from the temperature mapping exercise and by their proximity to one another.

Data loggers (with an alarm) will be placed in the storage areas associated with the highest temperature for each grouped area (worst case). The results from the data loggers will act as a guide for the other clinical areas within the group. *We recommend that areas within any hospital are grouped appropriately to balance the impact of investigating excursions and to ensure the resource required to monitor wards is minimal.*

The mean kinetic temperature (MKT) is a measure which allows the impact of transient excursions to be interpreted. The MKT will be continuously calculated in the worst case areas and in the unlikely event that the MKT exceeds 25°C a risk assessment will be performed. The risk assessment should encompass an evaluation of the total thermal stress experienced by the medicines throughout their lifespan and not solely on one excursion or ward temperatures alone. Temperature readings from pharmacy may also need to be taken into consideration to provide a full picture of the thermal stress the medicine has experienced. Based on the study performed in clinical areas it is unlikely that the MKT will exceed 25°C in our Trust.

The reduction of the products expiry date will be considered if there is deemed to be a pharmaceutical quality risk following the assessment. *The reduction should **not** be based on a single excursion but on the predicted duration of exposure of the medicines to high temperatures.* It is recommended that if an expiry reduction is deemed necessary following a risk assessment that a blanket reduction of e.g. 4 weeks should be applied to allow for further possible excursions. This should reduce the need to continually reduce expiry dates following multiple single excursions. The blanket reduction should be based on this guidance and temperatures should continue to be monitored to ensure the blanket reduction remains appropriate.

The above recommendations can only be applied to medicines stored in its original primary packaging. Any medicines not stored within original primary packaging that are subject to temperatures greater than defined in their SmPC should be disposed of and not used.

Step 6 – Reviewing the effectiveness of the action plan

The action plan will be reviewed following implementation to confirm that the designated worst case locations remain in the same area, a smaller scale mapping exercise will be undertaken periodically.

This project was performed in response to the NHS England document - Heatwave Plan for England 2013. Following the implementation of the action plan we will have a wealth of information and therefore assurance that we are correctly storing all medicines within clinical areas, including during periods of hot weather, a challenge that many NHS colleagues nationwide will also have to embrace. The information gained will also help inform our business continuity plan and ensure we are successfully prepared for climate change in the years to come.

For further information contact:

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