Controlled temperature storage of medicinals

Good practice measures in the community pharmacy

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What is an expiry date? Quite simply, it is an assurance that a medicinal product will meet applicable standards of identity, strength, quality and purity at the time of use.[1] However, this assurance is not all-encompassing; it is only applicable under the storage conditions specified by the manufacturer on the labelling and packaging following extensive stability studies. Failure to provide for the storage conditions specified by pharmaceutical manufacturers invalidates this assurance and consequently, it is the responsibility of manufacturers, distributors, importers and dispensing pharmacists to ensure that adequate provisions are taken in their premises in this regard throughout the shelf life of the product.

Stress factors and medicinal products

Stability is defined as the extent to which a product retains, within specified limits, throughout its period of storage and use, the same properties and characteristics that it possessed at the time of its manufacture. There are various stress factors that can accelerate loss of stability. In view of the importance of chemical degradation as a means of instability, and that underlying chemical or physicochemical mechanisms are often responsible for physical instability, the major stress factor is temperature, since increases in temperature cause increases in the rate of degradation of medicinal products. However, it should not be assumed that it is merely elevated temperatures that are detrimental to a product's stability. Excessively reduced temperatures can also cause loss of stability, such as by decreasing the solubility of solutes in a given solvent, while oscillations in temperatures can cause a change in particle size in suspensions (the Ostwald ripening effect), thus altering the dissolution profile and possibility the bioavailability of the product.

Labelling of medicinal products

Given the importance of proper storage of medicinal products, some attention should be paid to the labelling of medicinal products and the instructions given thereon. The determination of the expiry date of a medicinal product is a result of stability studies under long term, accelerated and, sometimes, intermediate conditions. The selection of the combinations of temperature and humidity are determined by the climatic zone within which the medicinal product is intended to be stored and distributed. In the early years of a product's market life, its shelf life is sometimes calculated by extrapolation of stability study data through statistical analysis. The availability of suitable data allows a fairly accurate shelf life to be determined. The situation is less certain when, at the time of application for a market authorization, the product has not shown sufficient degradation, or indeed no degradation, that will allow statistical analysis of the kinetics of degradation to generate a shelf life with a degree of certainty. Under both these circumstances a shelf life which is twice the length of the long term stability study carried out to date is allowed, up to a maximum of one year beyond the data obtained in the long term study.[2] Ongoing stability studies are subsequently undertaken post-marketing to monitor the product and confirm the validity of the labelled shelf life.[3]

Malta, being a Mediterranean country, falls within Climatic Zone II (Table 1). Unless other stress factors, such as relative humidity (RH), light and microbiological

contamination, have a more predominant effect on shelf life, products intended for storage in Climatic Zone II are tested under accelerated conditions at 40°C ± 2°C, 75% RH ± 5% RH for a minimum of 6 months, and under long term conditions at 25°C ± 2°C, 60% RH ± 5% RH for a minimum of 12 months.[4] The manufacturer also has the option of additional testing under intermediate conditions of 30°C ± 2°C, 65% RH ± 5% RH, or of carrying out the long term study under these latter conditions rather than those previously mentioned, particularly if the product is intended for export to a country in Climatic Zone III or IV.[5] The outcome of the stability study determines the labelling requirements of the finished product (Table 2). However, products that suffer from stability issues at lower temperatures will also bear statements to this effect ("Do not refrigerate or freeze").[6]

Good practice in the storage of medicinal products

The European Commission's Guide to Good Manufacturing Practice, with regards to storage areas, states that "Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.".[7] Similar provisions are also listed in the Commission's Guidelines on Good Distribution Practice: "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.".[8]

In the case of medicinal products which do not require special storage conditions (i.e. refrigeration or freezing), these two concise statements are based on the need to store medicinal products under conditions of controlled temperature without compromise to their stability and shelf life. The word "controlled" implies a degree of control over the temperature of the environment, such that extremes of hot and cold temperature are not encountered. This, in turn, also implies the need for some degree of periodic temperature monitoring using one or more appropriately-located, calibrated devices.

Application of good practice to community pharmacies

Based on meteorological data for 2004,[9] Malta's mean kinetic temperature was 20.3°C, with the lowest mean minimum temperature being registered in January (9.4°C) and the highest mean maximum temperature in July (31.0°C). Such ranges in temperature, whilst not excessive, are certainly not consistent with the concept of a controlled temperature environment, and therefore the installation of an air-conditioning unit to cool or warm the pharmacy is necessary. Most, if not all, pharmacies in Malta are already equipped with such a unit. However, one's faith in the ability of the unit to control the temperature in the desired location/s should not be a blind one. It should not be assumed that, merely because the remote control reads 20°C, the unit's thermostat is also accurately set to 20°C, neither that the unit is effectively maintaining a temperature of 20°C in all areas of the pharmacy. It is therefore recommendable to engage in a few simple good practice measures in this regard.

- Purchase one or two min-max thermometers. How many you need depends on the size and layout of the pharmacy. There are mercury-in-glass, ethanol and electronic types: choose one which you can read and reset quickly, easily, and with a minimum of fiddling about with various buttons.
- Have the accuracy of the thermometers checked for you at least once a year, either by the supplier or the local standards authority. If your thermometer is not accurate to within 1-2°C, you should consider replacing it. You should also request a certificate confirming the results of the validation and indicating the next validation date.
- Carry out some elementary temperature mapping to see whether the average temperatures of different areas of the pharmacy are the same. If you have a long dispensing counter, you might find that temperatures are different at the two ends of the counter, particularly if one end is close to the entrance. The same applies if you have some medicines behind the counter, and a stock of medicinal products in a separate store room or dispensing room, especially if air exchange between the two areas is limited or ineffective. If the two areas do not maintain similar temperatures (within 1-2°C of each other), install two thermometers, one in either location. Do not keep one thermometer, shuttling it between the two locations; it will completely defeat the purpose of min-

Table 1: International Climatic Zones and Climatic Conditions[10]

Climatic Condition	Zone I Temperate	Zone II Mediterranean (sub-tropical)	Zone III Hot/dry or Hot/moderate RH	Zone IV Very hot/humid
Mean Annual Temperature	<20°C	20.5 - 24°C	>24°C	>24°C
Kinetic Mean Temperature	21°C	26°C	31°C	31°C
Mean Annual Relative Humidity	45%	60%	40%	70%

max monitoring over a period of time and the possibility of adversely affecting the thermometer's accuracy will increase.

- Install the thermometers in a convenient place to read (avoid having to climb on a stool each time). Make sure the location of the thermometer is a valid one, that is, as close to the medicinal products as possible.
- Monitor the maximum and minimum temperatures at least once weekly, and reset the thermometers. Log your readings: if you don't keep a record that you did it, then you didn't do it!
- Analyse the data by calculating the monthly mean kinetic temperature. The mean kinetic temperature is that single (derived) temperature that, if maintained over a period of time, would provide the same thermal challenge to a drug product as would be experienced due to a range of both higher and lower temperatures for that same time period. It normally has a higher value than the arithmetic mean temperature and takes into account the Arrhenius equation for temperature dependence of reaction rate constants.[4] An example of a calculation of the mean kinetic temperature is shown in Table 3. It can be seen that, provided the number of temperature excursions outside the 20-25°C range is small, the effect on the chemical stability of the compound is equivalent to a constant temperature maintained within range. Check that the mean kinetic temperature falls within the desired range, namely 20-25°C, but also that the number of raw data temperature excursions outside this range is limited to an acceptably small number (no more than once or twice monthly).

Practice Points

- Purchase one or more min-max thermometers.
- Have the thermometers checked and certified regularly.
- Carry out temperature mapping.
- Install the thermometers in a convenient, valid location.
- Monitor the minimum and maximum thermometers weekly and log the data.
- Analyse the data by calculating the mean kinetic temperature.
- Manage the air flow in the pharmacy to obtain effective temperature control.

What if your mean kinetic temperature falls just outside the 20-25°C or the number of temperature excursions outside this limit is excessive? In most cases, the situation may be brought under control by simple measures aimed at controlling air flow in the pharmacy, thus increasing the effectiveness of your air-conditioning unit/s.

- Keep the door to the street closed as much as possible; an open door causes exchange of air between the street and the pharmacy, decreasing the effectiveness of your temperature control.
- If the medicines in your dispensing area are behind some form of partition, keep the partitions closed during opening hours, particularly in the summer months; this will reduce exchange of slightly warmer air from the pharmacy with the medicines; the same applies if you have a separate dispensing or store area.
- Try and promote air exchange between cooler and warmer parts of the pharmacy, especially if your air-conditioner is "over-effective" in one region and "under-effective" in another. This can be done by the use of a strategically located fan. Monitor the temperatures to see if your efforts are successful.
- Remember that temperature control applies also at night and on Sundays and public holidays; failure to do so will generate numerous temperature excursions from the required range. Try and exchange the remote control of your air conditioner for one which will allow you to program the unit to turn on and off at awkward times if this feature is not currently available. The judicious use of the air conditioner at key moments in the day or night will give a more effective temperature control than leaving the unit on or off indiscriminately. Moreover, this will reduce electricity consumption and increase the life of your unit.
- If one part of your pharmacy appears to have a slightly higher mean temperature which you cannot lower, then stock your medicines accordingly: place those with a "Do not store above 25°C" or "Do not store above 30°C" in the region of the pharmacy with better temperature control, and those with no particular storage requirements in the area with poorer control.

Table 2: Storage Statements on the Medicinal Product Label[6]

Testing conditions where stability has been shown	Required labelling statement
25°C / 60% RH (long term) and 40°C / 75% RH (accelerated)	None
30°C / 65% RH (long term) and 40°C / 75% RH (accelerated)	None
25°C / 60% RH (long term) and 30°C / 65% RH (intermediate)	Do not store above 30°C or Store below 30°C
30°C / 65% RH (long term)	Do not store above 30°C or Store below 30°C
25°C / 60% RH (long term)	Do not store above 25°C or Store below 25°C
25°C / 60% RH (long term)	Do not store above 25°C or Store below 25°C

Advice to the patient

Finally, remember to advise the patient as regards appropriate storage of medicinal products. The entire objective of all these measures is to guarantee the quality of the medicinal product when administered to the patient, who should in turn be encouraged to store medicinal products in a cool place. Nevertheless, the occasional patient will admit to having left medicinal products in a sunny place and will ask if the product is still effective. A fairly good rule of thumb is to remember that a 10° rise in temperature approximately doubles the rate of most reactions. Ultimately, however, the best advice to give stems from the pharmacist's professional common sense, taking into account the time of year, the duration of exposure and the medicinal product under consideration.

Table 3: Calculation of the Mean Kinetic Temperature[11]

$$\text{Mean Kinetic Temperature} = \frac{9982.68}{-\ln \frac{\sum e^{-9982.68/T}}{n}} - 273.16$$

T is the recorded temperature in Kelvin (°C + 273.16), n is the number of readings, ln represents natural logarithms, and e is the natural logarithm base.

Week	Minimum (°C)	Maximum (°C)	Average (°C)	Average (Kelvin)	$e^{-9982.68/T}$
1	20	24	22.0	295.16	2.05×10^{-15}
2	23	27	25.0	298.16	2.88×10^{-15}
3	19	23	21.0	294.16	1.83×10^{-15}
4	21	24	22.5	295.66	2.17×10^{-15}

$$\sum e^{-9982.68/T} = 2.05 \times 10^{-15} + 2.88 \times 10^{-15} + 1.83 \times 10^{-15} + 2.17 \times 10^{-15} = 8.93 \times 10^{-15}$$

$$\text{Mean Kinetic Temperature} = \frac{9982.68}{-\ln \frac{8.93 \times 10^{-15}}{4}} - 273.16 = 22.7°C$$

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