

**STORAGE, STABILITY AND
IN-USE SHELF-LIFE
GUIDELINES FOR
NON-STERILE MEDICINES**

Introduction

A pharmacist has a duty of care to the patients he or she dispenses or supplies medicines to, to ensure that those medicines and medical devices are both safe and effective and thus have not deteriorated due to the storage of these products within the Pharmacy. This is implicit within the Royal Pharmaceutical Society's Code of Ethics and Professional Standards⁽¹⁾.

The Code of Ethics notes that *"Materials must normally be stored in the manufacturer's original containers"*, that *"All materials must be stored under suitable conditions, appropriate to the nature of and stability of the material concerned"* and that *"A pharmacist must exercise his/her knowledge of stability of materials to segregate for disposal substances which have deteriorated (paraphrased)"* (Standard 5.7 i, ii and iii)⁽¹⁾.

However, this advice requires a degree of interpretation. For example, how many times is a manufacturer's original container intended to be opened? The expiry of a licensed medicinal product is validated for in-use conditions as part of the licence application but the information on the number of permitted openings of the container before validated storage conditions are exceeded will only be available from the manufacturer. Secondly, it is unreasonable to expect that a pharmacist could have the knowledge of the stability, degradation routes and degradation products of all the medicines he or she will encounter.

Fortunately much of the required knowledge can be dealt with by looking at the stability and storage requirements of different dosage forms in general (though, of course, as with any generalisation, there are always exceptions to the rule). For example with tablets and capsules, the MCA's guidance to the NHS with regard to unlicensed pre-packing⁽²⁾ is that for repackaging, a 12-month shelf-life can be applied (or the manufacturer's expiry if less). This shelf-life might also be then applied to opened containers of tablets. A 1-year shelf-life from the date of opening of a liquid medicine however would not necessarily be appropriate as other factors such as the presence or absence of a preservative or the loss of volatile ingredients need to be considered. These considerations will be dealt with more fully in the General Guidance section.

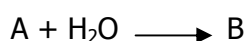
The aim of this guidance is to ensure that "in use" shelf-lives applied to medicinal products, once their primary packaging has been breached, are appropriate. One of the purposes of primary packaging is to help protect the product and prevent or reduce its degradation or contamination. This protection is diminished once the primary packaging of a medicinal product has been opened and thus "in-use" shelf-lives are on the whole greatly reduced when compared to the manufacturer's expiry.

Although these guidelines are primarily aimed at the sensible assignment of "in-use" shelf-lives for a range of products, the issue of whether medicines that have, or are suspected of having, been stored outside their required storage conditions is dealt with. Strategies for the assignment of reduced shelf-lives in such situations are discussed.

Stability Problems

The stability of a medicinal product relates to its resistance to various chemical and physical reactions and microbiological contamination or proliferation. This stability is expressed as the manufacturer's shelf-life, in which the product is predicted to remain fit for its intended purpose if stored correctly in its closed container. Commonly this shelf-life is defined as the time for the original potency of the active drug to be reduced to 90%. More stringent time limits may apply however if the degradation products of a drug are toxic (eg Tetracycline).

Chemical Kinetics is concerned with the rate and mechanism of chemical reactions. Application of chemical kinetic theory enables the rate of degradation of a drug to be calculated from stability experiments. The rate of such a reaction can be expressed in terms of the concentrations of the reactants and a rate constant. For example, Drug A which degrades by hydrolysis to Degradant B thus:



would be expressed in terms of its rate of reaction thus:

$$-\frac{d[A]}{dt} = K[A][H_2O]$$

or the decrease in the concentration of A with time is equal to the rate constant of the reaction K times the original concentrations of the reactants. This is called a rate equation.

Such rate equations determine the order of reaction, which forms a separate subject in itself (for more detailed information see the Pharmaceutical Codex⁽³⁾). The order of reaction reflects the relationship between the rate constant and the concentration of the reactants. This in turn governs the time to 10% degradation. Suffice it to say that most chemical degradations follow a first order reaction. Here the rate of the degradation is proportional to the initial concentration of the drug BUT the time to reach 10% degradation is dependant purely on the rate constant only. This of relevance with regard to the effect of temperature.

For most reactions, aside from photochemical degradation, a rise in temperature increases the rate of reaction and thus the rate constant. This in turn will decrease the time to 10% degradation. For example in many hydrolysis reactions the rate of reaction may triple with a 10°C rise in temperature⁽³⁾. This is of course of major importance with medicines whose storage is particularly temperature sensitive, eg refrigerated items.

Hydrolysis involves the reaction of a drug molecule with water which results in cleavage. Molecular structures prone to hydrolysis reactions include esters such as found in aspirin, amides such as chloramphenicol or lactam rings as in penicillins. Hydrolysis occurs not only in solution but in suspensions and solid dosage forms.

Oxidation reactions of pharmaceuticals are usually autoxidations⁽³⁾ rather than true reversible oxidation/reduction reactions. Autoxidations are irreversible chain reactions in which the drug substance becomes slowly oxidised in the presence of atmospheric oxygen. Examples of drugs prone to oxidation include morphine, adrenaline, dopamine, fixed oils and fats.

For liquid preparations oxidation can become problematic once the first dose of a liquid is removed from a container which may have had a relatively air tight closure. In withdrawing doses from a bottle the headspace and hence the amount of oxygen increases with each dose withdrawn. This can mean that the in-use shelf-life may be substantially shorter than the expiry of the unopened product (eg Morphine Sulphate oral solutions have a 90-day shelf-life on opening).

Another consequence of the increase in headspace and repeated opening of a bottle of a liquid pharmaceutical is that any volatile active ingredient or excipient will be progressively lost. The preservative efficacy of chloroform reduces rapidly with repeated opening of containers due to volatilisation. Losses of roughly 20 to 30% are observed after two weeks in 150 ml bottles opened on a daily basis to remove 5 ml doses of medication⁽³⁾⁽⁴⁾.

When exposed to light many drugs and excipients will degrade due to a variety of complex photochemical reactions. Ultraviolet light can often initiate the chain reaction that precipitates autoxidation (eg Chlorpromazine). However provided amber bottles are used, as is common practice, this should not be an overriding stability concern.

Liquid pharmaceuticals in particular can support the growth of micro-organisms. Aqueous solutions and suspensions and oil in water emulsions are especially suited to support microbial growth, whereas water in oil emulsions are less susceptible as here the oil continuous phase can impede growth. However microbial growth can also occur on solid dose forms, in particular moulds on tablets, if enough moisture is present.

The proliferation of micro-organisms is unacceptable. Firstly as the organisms and/or their endotoxins may be pathogenic to the patient and secondly as spoilage of the product will occur resulting in physical changes in the medicine (turbidity, discolouration, odours, gas formation, loss of viscosity or cracking of emulsions or creams etc). Mechanisms to control the proliferation of micro-organisms include the use of packaging and closures that minimises contamination of the product in use, presence of an antimicrobial preservative and utilising appropriate storage conditions. Microbial growth is inhibited by refrigeration, thus this is appropriate for unpreserved medicines. However, preservative efficacy increases with temperature so preserved medicines should not be refrigerated unless this is specified by the manufacturer.

Storage Conditions

Good practice requires that the storage areas for medicinal products are maintained within acceptable temperature limits for the medicines concerned and that temperatures are monitored regularly to demonstrate that these conditions continue to be met. It is important that for temperature sensitive medicines it can be shown that they can be delivered (if necessary) from the Pharmacy to the patient or outlying clinic under controlled conditions. That is, any cold chain arrangement can be proven to maintain adequate cold temperatures during transit.

The type of temperature monitoring devices used is governed to some extent by the type of facility or area being monitored. For small refrigerators and for warehouse areas a mercury or electronic maximum/minimum thermometer can be used in conjunction with a log book or other system of record keeping. Larger refrigerators

and walk-in units should be fitted with a continuous recording device such as a chart recorder or data logger⁽⁵⁾. The type of device used may also be governed by the expense and sensitivity of the products requiring defined temperature storage. For example, a multi-probe continuous monitoring system with alarm may cost several thousand pounds but may be far cheaper than the cost of replacing stock affected by prolonged out-of-limits storage.

Whichever type of temperature measuring device is used it should be calibrated regularly. For example an electronic thermometer's performance can be checked against a mercury thermometer (which complies with BS1704 as a minimum or BS593 supplied with BS or NAMAS certificate). Similarly a chart recorder on a large refrigerator can be checked against a temperature data logger. Any temperature alarm system, if fitted, should be tested at least annually to confirm it is operating correctly at both its high and low set points⁽⁵⁾.

For cold storage facilities, the temperature in small refrigerators should be checked at least daily. Larger refrigerators and walk-in units are monitored continuously. For ambient storage facilities, monitoring requirements again are dependant on the size and layout of the facilities. For a small warehouse the minimum requirement is to record maximum and minimum temperature weekly⁽⁵⁾. However there should be an awareness of areas where products may suffer adversely such as near to heaters or close to the roof in an uninsulated building. It is advised that the frequency of monitoring of ambient storage facilities should be increased during exceptionally hot and cold weather⁽⁵⁾.

It is important to have a knowledge of the temperature distribution within the cold storage facility. For a walk-in unit a temperature mapping exercise will identify where the hot and cold spots are, thus indicating the most appropriate places for temperature monitoring. This is also important in small refrigerators that may be filled to capacity and are not fan assisted. In these circumstances products placed next to, or in contact with the chiller plate will freeze. Temperature mapping (in the loaded state) should be repeated annually⁽⁵⁾. It is also important to determine the time it takes a refrigerator or cold storage facility to reach 8°C in the event of a power failure. The change in temperature during any defrosting cycle must also be established.

The maintenance of an effective cold chain must be demonstrable if temperature sensitive medicines are transported from the Pharmacy department to outlying clinics or other hospitals etc. A written procedure for the packing, issuing and transportation of such medicines should be available (as well as a procedure for the receipt of temperature sensitive goods into the Pharmacy). Such a procedure should describe the documentation process, the checking policy, the type of packing to be used and the loading pattern⁽⁶⁾. Loading patterns should be consistent and insulating filler material (eg polystyrene) used to fill spaces in incomplete loads.

Orders should be assembled in a cold room if available or if not then assembly must occur immediately prior to despatch. Dedicated rigid cool boxes should be used with commercial rather than domestic cold packs (such packs can be recycled from the deliveries of temperature sensitive products from ethical manufacturers). The use of frozen ice packs should be avoided unless it is possible to prevent such packs from coming into direct contact with the drug product⁽⁶⁾. The boxes should be labelled with "*Refrigerated Medicines - For Urgent Delivery*" or similar form of statement. The time the order was packed should also be recorded on the box. The longest routine

delivery undertaken should be used to validate the maintenance of the cold chain (temperature between 2 - 8°C). This can be achieved with the use of data loggers.

Storage Outside Specified Temperatures

There should be written procedures in place describing the action to be taken in the event of a loss of control over the storage conditions of temperature sensitive products, for example the accidental disconnection or breakdown of a refrigerator. These procedures should include the maintenance of suitable records as to the reason for the deviation (and its extent/duration) from the required temperature range, the products affected and the action subsequently taken.

Firstly the current temperature (and maximum and minimum temperatures) should be noted. The products affected should be transferred to a functioning cold storage facility, keeping them separate and identifiable from any unaffected stock. Attempts should then be made to establish how long the products have been outside the desired temperature range. Any evidence or previous lapses in required storage should be sought from the records kept of storage temperature deviations - including inspecting stock for any boxes previously marked "*Use First*".

Once the affected stock has been quarantined under appropriate storage conditions, then the following sources of information should be used to establish if the medicines are still suitable for use:

- Summary of Product Characteristics
- *The Fridge Database* by Julia Horwood and Stephen Wood (Medicines Information should have a copy or contact MI at Northwick Park)
- *Room Temperature Stability of Medicines Recommended for Cold Storage* by Paul Longland and Paul Rowbotham. The Pharmaceutical Journal 1989 **243**: 589 - 95
- Medical Information Department of the drug's manufacturer

Any stock that is still usable should be removed from quarantine marked as "*Use First*" and any reduced shelf-life should be applied in writing onto the packaging of the drug.

If no useful information is available to determine if a product is still suitable for use after exposure to an inappropriate temperature, then the application of Q_{10} values could be used. The Q_{10} value is the factor by which the rate constant, for the degradation reaction, increases for a 10°C rise in temperature. A pessimistic estimate of Q_{10} equals 4.

Calculations are based on the following equation⁽³⁾:

$$S_{(T_2)} = \frac{S_{(T_1)}}{Q_{10}^{\frac{(T_2 - T_1)}{10}}}$$

where S = shelf-life at temperature T.

As an example consider a product that requires refrigerated storage (take mean temperature as 5°C for convenience) and has 1-year of remaining shelf-life. The shelf-life at 25 degrees can be estimated using the above equation thus:

$$S_{(25)} = \frac{365}{4^{\frac{(25-5)}{10}}} = \frac{365}{4^2} = 23 \text{ days}$$

Such an approach should be used with caution as the value for Q_{10} may be greater than 4 or shelf-life may be governed by physical or microbiological stability. If the Q_{10} equation is to be used, then this should be in conjunction with a risk assessment with regard to the product in question. Such an assessment should consider the likelihood of any adverse effect caused by degradation (in conjunction with the route of administration) and the effect on the patient of any treatment failure associated with a lack of potency of the medicine.

Re-use of Returned Medicines

The re-use of medicines is covered by Standard 5.5 of Good Professional Practice in "*Medicines, Ethics and Practice*". Medicines brought in by patients are the patients' own property and under no circumstances should they be considered for re-use by anyone else⁽¹⁾. The storage history and conditions of such medicines is unknown and on self-medicating wards or for patients following a self-medication protocol, appropriate safeguards should be included in the policy to ensure that these medicines can be assessed as being fit for use. Such measures might include examining the dispensing date on the label to ascertain how long the patient has had the medicines in his or her possession.

Medicines which have been returned from the wards should be examined to assess their suitability for being returned to stock. There must be assurance (eg by QC monitoring of ward refrigerators etc) that the storage requirements of any returned ward medicines have been met, before such medicines are taken back into stock for re-use. There should be an appropriate local policy which deals with this issue.

General Guidelines for the Assignment of "In-Use" Shelf-lives

As noted in the introduction, the following recommendations for in-use shelf-lives are based on generalisations with regard to the dosage form of the medicine. As such there will always be exceptions to these rules and the use of professional judgement is still required. It is important that all medicines in bulk containers are dated on first opening so that such judgements can be made.

For oral solid dose forms, a date of one year from first opening⁽²⁾, or the manufacturer's expiry is less, is appropriate. This has been backed up on the whole by a study of repackaged medicines in various container types by the Trent QC Laboratory⁽⁷⁾. However care should be taken to identify those tablets which are susceptible to atmospheric moisture (eg Co-amoxiclav, Dipyridamol MR) or have a physical instability (eg volatility of GTN) as these tablets will require a shorter in-use shelf-life. This information can be elucidated usually from the packaging of the

medicine though the information is not usually prominent or by the presence of a desiccant in the container. However, it should be noted that with the increase in blister packaging and patient pack dispensing, the amount of tablets and capsules supplied in bulk packs is diminishing. For these unit dose forms of presentation, the manufacturer's expiry should be used unless the blister strip contains a desiccant (eg Nicorandil), in which case the in-use expiry on first opening the strip will be the normal length of time that a course of treatment takes to use up all the doses, ie one to two weeks.

For liquid medicines a distinction must be made between external and internal medicines and whether the liquid is preserved or not. For licensed liquid medicines, the licence holder must specify the storage conditions and any requirements as to the shelf-life in use. For example, reconstituted antibiotics will have specific defined storage and in-use shelf-life information on the label. However for all well preserved liquids, the manufacturer's expiry is validated to also cover normal in-use conditions and here the in-use expiry is not specified. For example, 30 openings and closings of a 150 ml bottle to withdraw 5 ml aliquots. What may require a degree of judgement is whether the withdrawal of doses is expected to be on a continuous basis once the bottle is opened (eg for a chronic condition) or on an occasional basis as required (eg for analgesia). As a general rule for preserved liquid medicines, a 6-month in-use shelf-life would be appropriate, though a local decision could be made to reduce this to 3-months for internal liquids⁽⁸⁾.

If anything is done to reduce the efficacy of the preservative (eg diluting with syrup or water for irrigation) then a much shorter shelf-life should be assigned. The Summary of Product Characteristics may give advice on suitable diluents and expiries but in the absence of information a conservative 2-week shelf-life⁽³⁾ should be applied.

As mentioned in the section on Stability Problems, above, mixtures preserved with chloroform will deteriorate on repeated opening due to the loss of volatilised chloroform in the headspace. Here the recommendation is that the in-use shelf-life is again only 2-weeks. It should be noted that this assumes that the unopened container was tightly closed originally.

Extemporaneously prepared liquid medicines which are compounded against a pharmacopoeial monograph are either to be freshly prepared or recently prepared. The definitions of both these terms are given in Part II of the General Notices of the B.P. "*Recently prepared*" indicates that deterioration is likely when the mixture is kept for more than 4-weeks at 15° to 25°C⁽⁹⁾. Where standard suspending base is used as the vehicle in an Eastern Region Extemporaneous Dispensing Specification, the in-use shelf-life of the product should again be 4-weeks. The efficacy of the preservative system used in standard suspending base has been validated to this length of time.

The in-use shelf-life for topical semi-solid medications is determined by factors such as packaging format, presence of preservative, whether cream or ointment and whether there has been any dilution of the original basis. As noted in the above section on stability, creams which are generally oil in water emulsions are much more prone to microbial contamination as the continuous aqueous phase is a much more favourable medium for growth than the fatty continuous phase of an ointment base. Therefore the in-use shelf-life of creams should be shorter than that for ointments even if a preservative is present.

For those semi-solid medicines which are sterile, the in-use shelf-life assigned should be a matter of professional judgement, based on the presentation, area of application and clinical use of the product. For example, sterile creams and ointments for application to wounds and burns should have an in-use shelf-life of 24-hours. For ophthalmic use, the shelf-life should either reflect the length of treatment (eg 5-days for antibiotics) or the local policy as to ward or domiciliary use, to a maximum of 4-weeks from opening for supplies against out-patient prescriptions (unless otherwise directed by the manufacturer).

For licensed creams and ointments, the following in-use shelf-lives should be applied. For ointments packed in tubes, an in-use shelf-life of 6-months should be applied, unless otherwise recommended by the manufacturer. For creams packed in tubes, a shelf-life of 3-months from first opening should be applied, though local policy may direct 1-month only for unpreserved creams, again the manufacturer's guidance on in-use expiry takes precedence. For ointments packed in jars and pots, the in-use shelf-life should be reduced to 3-months whereas creams should have an in-use shelf-life of 1-month from first opening.

The BNF recommends that licensed creams and ointments should not be diluted⁽¹⁰⁾. The use of an unsuitable diluent can decrease the bioavailability of the drug or adversely affect the stability of the preparation. In particular the microbiological stability can be compromised if the diluent does not contain a preservative or if the preservative is incompatible with the product. This is a particular importance for diluted creams if the preservative does not partition sufficiently into the continuous aqueous phase. Diluted ointments should have an in-use shelf-life of 4-weeks and diluted creams, 2-weeks⁽⁹⁾. It should be noted that there are licensed ready diluted steroid creams and ointments available. For these products the general guidelines for creams and ointments (undiluted) apply.

For extemporaneously prepared creams and ointments prepared from standard bases, the following expiries should be applied (in the absence of any validated stability study). For ointments a maximum expiry of 8-weeks from date of manufacture should be applied and for creams a maximum expiry of 4-weeks from the date of manufacture.

IN-USE SHELF-LIVES

NOTE: THE MANUFACTURER'S EXPIRY, IF SHORTER OR THE MANUFACTURER'S SPECIFIED IN-USE SHELF-LIFE TAKES PRECEDENCE OVER THE FOLLOWING GUIDELINES. THE GUIDANCE GIVEN HERE SHOULD BE USED AS AID TO THE PHARMACIST'S OWN PROFESSIONAL JUDGEMENT ON MATTERS OF STABILITY AND IN-USE EXPIRY

TABLETS AND CAPSULES

Blister Packed/Single Unit Dose	Manufacturer's Expiry
Bulk Packs	1-Year from date of opening
Exceptions: Products susceptible to atmospheric moisture, GTN	

LIQUIDS

Preserved	Internal and External 6-Months (local policy may direct 3-months for internal liquids)
Extemporaneously Prepared to a BP Monograph or EDS Formula	4-Weeks from date of manufacture
Diluted Preserved liquids	2-Weeks
Preserved with Chloroform	2-Weeks

CREAMS

Packed in Tubes	3-Months (local policy may direct 1-Month for Unpreserved creams)
Packed in Jars/Pots	1-Month
Diluted Commercial Preparations	2-Weeks
Extemporaneously Prepared in a suitable base	4-Weeks from date of manufacture

OINTMENTS

Packed in Tubes	6-Months
Packed in Jars/Pots	3-Months
Diluted Commercial Preparations	4-Weeks
Extemporaneously Prepared in a suitable base	8-Weeks from date of manufacture

REFERENCES

- 1: Anon. (July 2000) *Medicines, Ethics and Practice, A Guide for Pharmacists. 24th Edition* London: Royal Pharmaceutical Society of Great Britain. pp 85-86
- 2: Anon. (September 1992) *Guidance to the NHS on the Licensing Requirements of the Medicines Act 1968* London: The Medicines Control Agency. Section 4.10
- 3: Lund W ed (1994) *The Pharmaceutical Codex. 12th Edition* London: The Pharmaceutical Press. pp 277-86 and 306-9
- 4: Allwood M C and Shaw R J S (1987) *Preservatives in the Food, Pharmaceutical and Environmental Industries - Technical Series 22: Society for Applied Bacteriology* (Blackwell Scientific Publications). pp 197 - 208
- 5: Viner J ed (January/February 1997) *MAIL 99th Edition* London: The Medicines Control Agency. pp 2-3
- 6: Anon. (April 1999) *The Vaccine Cold Chain from Manufacturer to Patient: Guidance for the Storage and Transport of Vaccines* Northern and Yorkshire NHS Region: Regional Review Group for Communicable Disease Control. pp 6, 8 and 9
- 7: Sprake J M and Parkinson R (September 2000) *Shelf-Lives of Tablets and Capsules Repacked into Various Types of Container. Pharmacy Quality Control Laboratory Testing Report.* Trent: Quality Control Laboratory, Nottingham City Hospital
- 8: Anon. (November 1998) *In-Use Self-Lives of Medicines - Version 1* QAInfozone Website: www.qainfozone.org/members/faq-s/faq6/faq6.html (registration may be needed) pp 1 and 2
- 9: Anon (1998) *British Pharmacopoeia, Volume II* London: The Stationery Office pp 1400, 145, 1459
- 10: Anon (September 2000) *British National Formulary 40th Edition* London: The Pharmaceutical Press p 509

