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August 2024

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Assessing medicines when stored outside manufacturer recommendations

Storage of medicines per manufacturers' specifications ensures medicines are fit for purpose. If stored outside these specifications, or used beyond the expiry date, medicines may be less effective, and/or have increased toxicity. This bulletin provides a framework for considering whether medicines stored for short periods outside manufacturers specifications remain suitable for use.

The main factors that impact stability of medicines are temperature, moisture, and light. Pharmacists may need to consider using medicines which have been stored outside manufacturer's specification.

Examples may include:

- Medicines needed in an emergency (e.g. a poisoning antidote) when the only medicine available may have recently expired.
- Short term storage at elevated temperatures will increase rate of degradation of the medicine (e.g. after a brief electricity outage to a refrigerator).
- Medicines stored at high humidity may undergo increased rates of degradation due to hydrolysis (e.g. loose tablets stored without desiccant in a compliance aid in humid conditions).
- Medicines stored outside of light-protective packaging may undergo photodegradation (e.g. tablets removed from blister packaging when added to compliance aids).

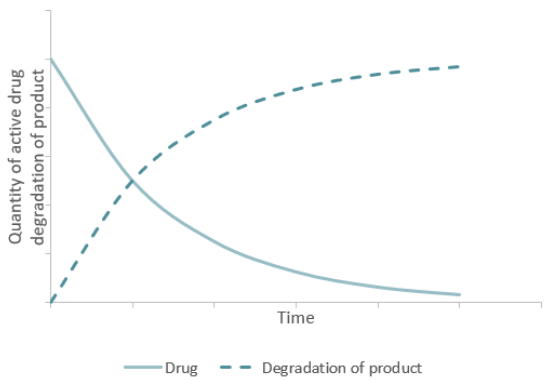
As discussed below most medicines may be stored incorrectly for short periods without significantly effecting the quality of medicine, however if medicines have been stored for extended periods under incorrect conditions contact the manufacturer to determine suitability of using the medicine.

Expiry Date Considerations

Medicines are required to comply with pharmacopeial specifications for the content of the active ingredient (also known as the Active Pharmaceutical Ingredient, API) typically needing to remain within 5% of the labelled strength throughout their shelf-life. For most medicines if the content of the active ingredient were to fall below pharmacopeial limits this is unlikely to be clinically significant.

Medicines will slowly degrade to known degradation products. Pharmacopeial specifications for medicines also place limits on their degradation products. For most medicines the degradation products are assayed as a method to measure drug degradation, with most degradation products having minimal activity or toxicity. Exceptions include meropenem, isoniazid, and pethidine where their degradation products may be toxic if administered in high doses and/or for prolonged periods[1].

The rate of degradation of the active ingredients and formation of the degradation products can both be predicted with complex equations such as the Arrhenius equation. For most medicines stored at a constant temperature the rates will follow first orders kinetics as per the chart[2]



As Pharmacopeial limits are typically 5%, only the initial portions of this graph are applicable. During this period the degradation of the active drug and the formation of the degradation products can be assumed to be almost linear. For example, if a product has a shelf-life of three years, to remain within specification it may degrade at an almost constant rate to have degraded by 5% over three years. Beyond this period the rate of degradation will gradually slow so that after six years there would be less than 10% degradation (i.e. 3 years after the product had reached its stated expiry date more than 90% of the drug would still be present). In developing countries, and in emergency situations the World Health Authority (WHO) suggest medicines may be used for at least 1 year after the manufacturers labelled expiry date[5].

If considering use of a medicine after its expiry date (e.g. in a poisoning situation when the only antidote available has expired) consider how long it is since the medicine expired. If close to the expiry date the medicine is likely to be very close to the pharmacopeial limits and remain suitable for use, but after longer periods the medicine may have reduced efficacy.

If considering use of a medicine beyond its expiry date the risks of potentially reduced efficacy versus the benefits of continuing therapy should be discussed with the prescriber. The risk may be lower for a medicine where its effects may be readily measured (e.g. heart rate or blood pressure) or serum concentration measured as dose adjustments may be guided by response.

Assessing the effects of short-term storage of medicines at incorrect temperatures

Temperature affects stability of medicines. The rate of degradation of the active drug and the formation of degradation products will both increase as the storage temperature is increased. This effect is used by manufacturers to predict stability. During initial development of medicines, stability can be predicted using accelerated stability testing, where an approximate guide is:

- For medicines intended to be stored in a refrigerator (2-8 °C), stability will be halved when stored at room temperature (25 °C).
- For medicines intended to be stored at room temperature, stability will be halved when stored at 40 °C[3].

Therefore, medicines intended to be stored in a refrigerator, will degrade faster if stored at room temperature, and if left permanently at room temperature, the shelf-life will be halved (i.e. if a product had a 3-year shelf-life in a refrigerator, the shelf-life would reduce to 1 ½ years if stored at room temperature). As degradation is approximately linear during this period, a temporary refrigerator outage with medicines stored at 10-15 °C for a few hours (as typically occurs following a short power outage) will generally have negligible effects on the long-term stability of the medicine.

Other sources suggest that the effects of short-term storage at elevated temperatures may be estimated by allowing for every 10 °C above the recommended storage temperature, the shelf life be reduced by twice time the product was stored at this temperature[4].

For example, if a product intended for storage in a refrigerator (2 to 8 °C) was stored for 6 hours at room temperature (25 °C), then the reduction in shelf life may be calculated as:

2x (time spent at each 10 °C above 2-8 °C, i.e. approximately 2x 10 °C intervals)
= 2x 2x 6 hours
= 24 hours (1 day)

i.e. The original expiry date should be reduced by 1 day, insignificant for most medicines with a 3 year expiry. However, if the temperature dropped below 0 °C, medicines may freeze or denature which will affect their physical stability and medicines may need to be discarded as:

- Medicines in a liquid formulation may not dissolve or disperse when the frozen liquid is thawed.
- Emulsions may crack, separating into aqueous and oil components, which may not re-form as a stable emulsion on shaking.
- Conformation of proteins (e.g. insulins, monoclonal antibodies) may be altered and reduce their pharmacologic activity.

The Specialist Pharmacy Service, UK, has a useful tool to assess stability of refrigerated medicines after temperature excursions, see https://www.sps.nhs.uk/home/tools/refrigerated-medicines-stability-tool/

NB: Vaccines are biological products containing proteins which are very sensitive to both freezing and heat. To ensure vaccines remain potent they must always be stored correctly. For any temperature excursions check with your local vaccine coordinators.

Humidity and Light

Light and humidity may also affect the rate of degradation for some medicines. Medicines sensitive to light will undergo rapid degradation if exposed to light, while high humidity may reduce chemical and physical stability of some medicines (particularly those in solid dose forms e.g. tablets). A full description of these effects has not been included in this Bulletin.

References

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