Specialist Pharmacy Service

NHS Pharmaceutical Quality Assurance Committee and UK Ophthalmic Pharmacist's Group

Guidance on the in-use shelf life for eye drops and ointments

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UKOPG

NHS Pharmaceutical Quality Assurance Committee

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Summary

This document takes a risk based approach to assigning the in-use shelf-life for eye drops used in UK hospitals based on the risks of the patient population, the risk of microbial contamination and the risk of microbial proliferation. It is set out as a best practice recommendation, to apply to both eye drops supplied as medicines and as Medical Devices. Where a manufacturer specifically recommends a shorter in-use shelf life this should be adhered to.

Background

The BNF (British National Formulary) is one of the main sources of information regarding policies and procedures for the use of medicines used in the UK. The BNF states that *eye-drops in multiple application containers for domiciliary use should not be used for more than four weeks after first opening (unless otherwise stated by the manufacturer). Multiple application for eye drops for use in hospital wards are normally discarded one week after first opening – local practice may vary*. It goes on to state that *separate container should only be supplied for each eye if there are special concerns about contamination, also that a fresh supply should be provided on discharge from hospital.* All eye drops must be sterile on initial supply / use.

The British Pharmacopoeia (BP) states for labelling requirements, in the eye preparations monograph, '*The label states, for multi-dose containers, the period after opening the container after which the contents must not be used. This period does not exceed 4 weeks, unless otherwise justified and authorised*'.

Furthermore an article published in the Pharmaceutical Journal in 2001[1] titled 'Guidance for use of ophthalmic preparations in hospital and care homes' is the source of the 14 day in-use shelf life that some hospitals still apply (possibly based on the below article reference 2). This included both inpatient and post-discharge use, the article also suggested single use containers be used in operating theatres, ophthalmic emergency departments and outpatients.

Livingstone et al[2] published an evaluation of an extended (14 day) period of use for preserved eye drops in hospital practice following a study evaluating the residues of eye drops post inpatient use. This showed an increase in contamination after 14 days compared to seven days but not at a statistically significant level (9.1% contamination after 14 days use). This paper references a paper by Harte et al[3] which showed a much higher contamination in eye drops presented in glass bottled with a separate dropper. This is perhaps not surprising due to the size of opening and the additional surface of the dropper exposed during use.

Rahman et al[4] looked at microbial contamination of unpreserved eye drops in multiple use containers, this looked at both inpatients' eye drops after three days and outpatients' eye drops after 7 days . Of the 53 antibiotic eye drops tested none were found to be contaminated, for other eye drops the contamination rate was 19%. The bottles used in the study were presented in glass bottled with a separate dropper.

This advice to the NHS has been consistent for some time and has not been updated in line with changing practice such as patient self-administration in hospitals, the use of patients own drugs and also the availability of CE marked Medical Device eye drops (for example artificial tears) and more recently licensed eye drop preparations in specialist containers where a longer in-use shelf life is supported by the manufacturer. However CE marked device shelf lives are viewed by MHRA licensing to be not evidence based. Numerous attempts to licence medicines in these containers, with a greater than 28 days in-use shelf life had failed due to a lack of evidence on the potential for biofilm formation during prolonged use, whether the fluid pathway post the silver spring (providing disinfection) remains wet or dry. There are now some unpreserved eye drops in bottles with a specialist self-closing tip design incorporating silver in the tip to reduce risk of microbial contamination, these do have a 28 days in-use shelf life within the Summary of Product Characteristics (SmPC)[5] and one product has recently been launched with a two month in-use shelf life[6]

Preservative efficacy testing

The BP does contain a test protocol for Efficacy of Antimicrobial Preservation (Appendix XVI C), the test consists of challenging the preparation, in its final container, with a prescribed inoculum of suitable micro-organisms, storing the inoculated preparation at a prescribed temperature, withdrawing samples from the container at specified intervals of time and counting the organisms in the samples so removed. The preservative properties of the preparation are adequate if, in the conditions of the test, there is a significant fall or no increase, as appropriate, in the number of micro-organisms in the inoculated preparation after the times and at the temperatures prescribed.

This test does present very much a worst case scenario as the preparation is deliberately contaminated with relatively high numbers of micro-organisms and a reduction in these

numbers must be seen over time (minimum 3 Log_{10} reduction for bacteria in 7 days and 1 Log_{10} reduction in fungi over 14 days, with subsequently no increase at day 28). This test is not really suitable for unpreserved eye drops unless the active drug or other excipients have anti-microbial activity.

For preserved eye preparations this represents a stern test and all licensed preserved eye preparations would have passed this test (this is assessed at product licensing), it is up to the end user to ensure themselves that preserved eye preparations supplied as unlicensed Specials have been tested in this way and comply with the test.

For unpreserved eye preparations, unless evidence is supplied by the manufacturer, it is difficult to gain assurance that the product will not become contaminated during use and hence in-use periods should be kept to a minimum. Some unpreserved eye drops are now supplied in containers designed to prevent contamination getting into the bottle and these may be assigned a longer shelf life if this is supported by the manufacturer (i.e stated in SmPC or patient information for Medical Devices.

This document aims to set out pragmatic advice on the use of multiple application eye preparations within hospitals to ensure a more consistent approach which is safe for patients but also does not waste valuable resources. The document covers both preserved and un-preserved eye preparations supplied as licensed medicines, unlicensed medicines (Specials) and CE marked Medical Devices.

Risk issues

Within this document a risk based approach has been taken to assign suggested maximum in-use shelf lives for eye preparations in various scenarios, these are set out in the table below. Overall it is difficult to see why the general hospital ward environment should be seen as presenting a higher risk of contamination of eye drops than the domestic environment although there may be specific wards where this may be felt to be the case. As discussed above the type of bottle can also have a significant impact with self-closing containers a lower risk than standard bottles with integral droppers and these are lower risk than glass bottles with separate droppers.

In terms of patient risk, then there are clearly enhanced risks post eye surgery, penetrating eye injury or in the case of severely dry eyes and hence a different approach is needed for post-surgery or damaged eyes than for normal eyes. Similarly if a patient already has an eye infection and is being treated with antimicrobial eye preparations, maybe alongside other eye preparations, there is also an enhanced risk should the preparation become contaminated (and possibly an increased risk of the preparation becoming contaminated from contact with the infected eye).

Unpreserved eye drops also present a bigger risk of microbial proliferation within the preparation and in-use shelf life for these preparations is normally restricted to an absolute

maximum of seven days when they are stored in the refrigerator, unless there is no risk of contamination occurring in the first place. The risk of microbial proliferation can be expected to be lower in eye drops with antimicrobial action such as those containing broad spectrum antibiotics. The British Pharmacopoeia states '*If eye drops do not contain antimicrobial preservatives they are supplied in single-dose containers or in multidose containers preventing microbial contamination of the contents after opening*'.

Recommended in-use shelf life for eye preparations used in NHS hospitals

The following information is provided for guidance only and it does not over-rule policies which may be in-use locally, furthermore if the manufacturer recommends a shorter shelf life this should take precedence over this advice. Where unpreserved preparations are presented in bottles which prevent contamination entering the product the manufacturer's recommendation (label claim / in the supporting literature) can be followed, although moderate and above risk this should be restricted to a maximum seven days in-use period.
Patients own eye preparations should only be used whilst they are an inpatient where these are clearly within their in-use shelf-life period as set out in the table; otherwise a fresh supply should be made. For patients admitted with an eye infection a fresh supply is recommended.

When a patient is discharged from hospital their eye preparations should be assessed for suitability to supply the ward used pack or whether a fresh supply is needed. This will depend on patient specific risks and the period of use of the eye preparations in the hospital.

Under all circumstances eye preparations must only be used for a single patient and single use eye drop containers should only be used once, although they can be used for multiple drops over a short period of time (up to one hour) such as for pre-surgery dilation regimes.

A separate bottle for each eye is generally not required, although may be requested if there is deemed a high patient risk of cross infection.

Paraffin based eye ointments can be treated in the same way as preserved eye drops.

Risk rating	Scenario	Preserved eye preparations	Un-preserved multi-use eye drops
Low risk	General ward Patient with no eye infection	28 days	28 days if within the product SmPC Otherwise 7 days stored in a refrigerator between use or 24 hours if stored at room temperature
Moderate risk	General ward Patient with eye infection* or higher risk ward environment	28 days	7 days for bottles with integral droppers, 24 hours for bottles with separate droppers both stored in a refrigerator between uses 14 days where this (or longer) is supported by the product manufacturer in the SmPC Otherwise Single use
High risk	During eye surgery	Not recommended	Single use only+
High risk	Inpatient post eye surgery or penetrative eye injury	7 days	24 hours if stored in the refrigerator Otherwise Single use only
	Use in out-patients and emergency departments Diagnostic dye preparations	Single use only+	Single use only+
	Patients home*	28 days Longer if specified in the SmPC	7 days stored in a refrigerator between use or 24 hours if stored at room temperature 28 days (or two months[6]) if within the product SmPC

* Further restrictions should be considered for patients with severe sight threatening eye infections

Follow the storage directions on the label or in the SmPC or package insert.

+ Where a single dose unit eye drop isn't available (no suitable product or temporary shortage), use of multi-dose bottles can be considered using aseptic technique and in accordance with a locally agree policy

References

1. Guidance for use of ophthalmic preparations in hospital and care homes part of New Guidance on use of eye preparations PJ Vol. 267 No. 7163 p. 307 (September 2001)
2. Evaluation of an extended period of use for preserved eye drops in hospital practice, D J Livingstone, G W Hanlon, S Dyke; Br J Ophthalmol 1998:473 – 475
3. Microbial contamination in residues of ophthalmic preparations, V Harte, M o'Hanrahan, R Timoney; Int J Pharmaceut 1978:1: 165-71
4. Microbial contamination of preservative free eye drops in multiple application containers: M Q Rahman, D Tejwani, j A Wilson, I Butcher, K Ramaesh: Bj J othalmol; 2006:2: 139-41
5. Example : Eysano 2.5 mg/ml eye drops SmPC, https://www.medicines.org.uk/emc/medicine/33235
6. COSOPT iMulti 20 mg/ml + 5 mg/ml eye drops, solution, https://www.medicines.org.uk/emc/product/9765