Are quality standards being reduced as eye drops are classed as devices?

Lucy Titcomb takes a look at the anomalies surrounding the classification of ophthalmic preparations

In March 2009, the Royal Pharmaceutical Society published “Practice guidance: medical devices”.1 In this guidance it advised that pharmacists, when deciding to purchase a medical device for retail sale, should ensure inter alia that it is CE marked, that it is suitable for its intended use or purpose and that instructions for its use are appropriate and easy to read.

Although not listed among the examples given in the guidance, there are now many artificial tear eye drops classed as devices rather than medicines. Pharmacists are now purchasing these CE-marked eye drops not only for over-the-counter sale but, since April 2008, to fill NHS prescriptions. The eye-drop devices in question are listed in the Drug Tariff in “part IXA — appliances” and may therefore be prescribed by GPs, dentists and non-medical prescribers. Ten new eye-drop devices have been added to this section since the end of 2008 and the list now contains 18 eye drops.2

Manufacturers wishing to supply appliances and chemical reagents for NHS prescribing must first seek approval from NHS Prescription Services for inclusion of a product in part IX of the Drug Tariff.3 Applications must meet the following three criteria for inclusion:

- The products are safe and are of good quality
- They are appropriate for GP and, if relevant, non-medical prescribing
- They are cost-effective

The eye-drop devices listed in the Drug Tariff are shown in Panel 1.

Single dose, preservative-free

The Drug Tariff listing for single dose, preservative-free eye drop devices includes the words “single dose unit”. The instructions for use of Vismed (TRB Chemedica), Systane (Alcon), Hydromoor (Moorfields Pharmaceuticals) and Blink Intensive Tears (AMO) comply with this standard. Lumecare Tear Drops single dose units are not yet available. Product literature for these products includes phrases such as “does not contain preservatives, any solution not used immediately after opening should be discarded”, “do not reuse, once opened, discard” and “always use fresh solution, discard the container and remaining solution immediately after use”. However, instructions for the other two single dose products are less strict. Those for Clinitas (Altacor) include the statement “the eye drops do not contain any preservatives; so after use, dispose of the container, in an environmentally friendly manner, even though it may not be completely empty.” A user wondering...
whether this means after single or multiple use of the resealable container will find rather vague guidance on the product website.14 The individual units of Clinitas lose their sterility when opened, the individual units can be resealed by turning the cap upside down, however as the product contains no preservative it should be discarded after short term use.14 There is no definition of “short term use”. Instructions for Ocusan (Agepha) are more specific: “The ampoule can be resealed and reused for up to 12 hours after first use. Discard ampoule 12 hours after 1st use.”14

Is this a safe practice? In a review of the literature on microbiological contamination of eye drops, Schlecht15 includes studies reporting contamination rates of over 32 per cent in bottles of unsealed eye drops. Although single dose units were not contaminated during a 24-hour evaluation of spontaneous contamination of ocular medicines in studies by Marchese et al16 and Su et al17 the former authors, who also inoculated a range of single dose units with bacterial and fungal pathogens, found only very small reductions in viable counts of Staphylococcus aureus and Pseudomonas aeruginosa over 24 hours in jaluronate (=hyaluronic acid), the only artificial tear product tested. This was in contrast to single dose units containing ketotifen, pilocarpine and tetryzoline-feniramine (=tetryzoline-pheniramine) in which the number of colony forming units of the bacteria studied were reduced by over 3 log units within 24 hours. This indicates that these drugs possess some antibacterial activity while the artificial tear does not.

Rahman et al18 found that 60 per cent of samples of multidose preservative-free bottles of hypromellose were contaminated following use over three or seven days. The authors conclude that preservative-free eye drops in multiple application containers are at risk of contamination with potentially pathogenic micro-organisms. They stated that this may place some patients at increased risk of developing serious ocular infections and that the prescription of these drops to patients with compromised ocular surface defences needs to be considered with caution.

Kim et al19 studied the microbial contamination of preservative-free artificial tears in reclosable containers over a period of 10 hours and concluded that they are at risk of contamination in a daily and multiple use setting, especially in patients with a poor administering technique, which is associated with fingertip touch and advanced age.

Schlecht15 evaluated microbiological contamination of preservative-free eye drops following proper and improper administration techniques and found contamination rates of over 80 per cent on multiple use when the dropper tip touched the conjunctiva, cheek or hand during twice daily administration for five consecutive days.

While the in-use period studied by Rahman et al18 is greater than the in-use shelf life proposed by the manufacturers of Ocusan, Kim’s study over 10 hours shows that the potential for contamination is a real one. Although this could be dangerous in certain patients the product’s instructions do not contain any warning against multiple use in patients with compromised eye who are at risk of ocular surface infection.

### Multidose, preservative-free

Some of the eye drop devices included in the Drug Tariff — Hyabak (SpectrumThea), Hylo-Care, Hylo-Forte, Hylo-Tear (Scope Ophthalmics) and Vismed Multi (TRB Chemedica) — are multidose, preservative-free preparations in which the contents of the bottle are protected from contamination by the innovative design of the delivery device. Hyabak is presented in the ABAK system, which contains a 0.2micron nylon fibre membrane that filters the solution. Pressure exerted on the bottle causes the solution to pass through the antibacterial filter in the ABAK system, forming a drop that falls from the tip of the dispenser. When pressure is released, the solution is reabsorbed and filtered from bacteria and air, ensuring the protection of the solution throughout its use.14 The effi-
Panel 2: Eye drops available in the COMOD and ABAK systems

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Available in:</th>
</tr>
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<tbody>
<tr>
<td>Cetotrilol</td>
<td>Carteabak</td>
<td>France, French overseas territories, Netherlands, Portugal, Italy</td>
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<tr>
<td>Diclofenac</td>
<td>Dicloabak</td>
<td>Belgium, Netherlands, Spain</td>
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<td>Filmabak</td>
<td>Belgium, Italy, Netherlands, Poland, Portugal, Spain, Switzerland</td>
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<td>Fluidabak</td>
<td>Mix-COMOD</td>
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<td>Wet-COMOD</td>
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<tr>
<td>Sodium cromoglicate</td>
<td>Allerg-abak</td>
<td>Netherlands</td>
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<td>Sodium hyaluronate</td>
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<tr>
<td>Sodium hyaluronate</td>
<td>Hylo-COMOD</td>
<td>Russia</td>
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<tr>
<td>Timolol maleate</td>
<td>Timabak</td>
<td>Germany, Brazil, Burkina Faso, Cameroon, Congo, France, French overseas territories, Gabon, Guinea, Hong Kong, Korea, Morocco, Philippines, Portugal, Senegal, Singapore, Spain, Tog</td>
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<td>Timo-COMOD</td>
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<tr>
<td>Timopos-COMOD</td>
<td>Germany*</td>
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<tr>
<td>Xylometazine HCl</td>
<td>Xylo-COMOD</td>
<td>Austria, Czech Republic, Germany, Netherlands, Turkey</td>
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* Discontinued or no longer marketed in this country

Articles

Panel 2: Eye drops available in the COMOD and ABAK systems

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<td>Austria, Czech Republic, Germany, Netherlands, Turkey</td>
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The British National Formulary states: “Eye drops in multiple-application containers for domiciliary use should not be used for more than four weeks after first opening (unless otherwise stated).” The BNF does not enlarge upon the words “unless otherwise stated” but this may relate to the European Pharmacopoeia’s reference to labelling of multidose containers stating that the label must include the following: “The period after opening the container after which the contents must not be used. This period does not exceed four weeks, unless otherwise justified and authorised.”

This advice appears to be prudent when one considers the results of a study by Geyer et al in which 19 per cent of multidose bottles used by glaucoma patients for up to eight weeks were contaminated while those used for periods of more than eight weeks were contaminated in 40 per cent of cases.

One multidose, preserved eye drop device listed in the appliances section of the Drug Tariff, Lumecare Long Lasting, contains carbomer 0.2 per cent with cetrimide as the preservative and is, therefore, similar to some medicinal products Liposic and Viscoatem. Product documentation for Lumecare Long Lasting includes the instruction to discard the contents 28 days after first opening.

Another, PVA 1.4% Tubilux, contains polyvinyl alcohol 1.4 per cent with Oxyl (Oxyd 0.025 per cent). Although it contains a preservative from the medicinal products Liquifilm Tears and SNO Tears, which each contain benzalkonium chloride and disodium edetate, it is also given an in-use shelf life of 28 days.

Conversely, other multidose, preserved eye drop devices listed in the Drug Tariff have longer “user lives” ranging from 45 days to six months (see Panel 1). All these products contain preservatives, but not ones with which most pharmacists are familiar. The current BNF does not list the preservatives in Optive, Oxyal or Systane.” Martindale does not list the preservative Oxyl (in Oxyal and PVA 1.4% Tubilux).

Polichloride chloride (PolyQuad) the preservative in Systane is only listed as an ingredient of a contact lens product marketed in Mexico for wetting, disinfecting and storage of gas-permeable and hard contact lenses and Octure (in Blink Intensive Tears) as an ingredient of Blink products marketed in Argentina and Australia.

Purite (in Optive) can only be found in Martindale in the title of a reference for a study comparing efficacy and safety of brimonidine-purite, an Allergan product not licensed in the UK. Oxyl and Purite are brands of stabilised oxychloro complex, a “disappearing” oxidative preservative that breaks down into sodium chloride and water when exposed to light. Purite consists of an equilibrium mixture of reactive chlorine species: 99.5 per cent sodium chloride and water, 0.5 per cent sodium chloride and trace amounts of chloride dioxide, which have bac-
tericidal, fungicidal and virucidal activity. Polidronium chloride (Polyquad) is an amni-
on surfactant preservative widely used in contact lens solutions.

Are such extended user lives justified for these products? How are pharmacists able to ensure that these eye drops are suitable for their intended use and that instructions for use are appropriate?

Preservative efficacy testing

The European Pharmacopeia (PhEur) specifies that ophthalmic preparations should be sterile. Formulations of multidose eye drops include one or more antimicrobial preservatives to reduce the number of organisms in the eye drops should contamination occur during their period of use.

Preservatives used in eye drops licensed as medicines in the UK are required to meet the test for efficacy of antimicrobial preservation as specified in the PhEur. For parenteral and ophthalmic preparations, the standard A criteria are that the reduction in the count of bacteria (specified strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*) with which a sample has been inoculated to a concentration of $10^5$ to $10^6$ cfu/ml must be log $2.0$ within six hours and “no increase” at 24 days (A criteria).

Although the A criteria standards for fungal organisms have not changed since the days of an independent British Pharmacopoeia (BP), those for bacteria are less stringent than those specified in the past. For example, the 1980 edition of the BP required that the number of bacteria recovered reduced by a factor of no less than $10^3$ within six hours of challenge and no organism is recovered at 24 hours and thereafter.

However, the PhEur criteria are more stringent than those applied by the United States Pharmacopoeia (USP) in which organisms are introduced into a sample of the preserved solution to be tested to give a final concentration of $10^5$ to $10^6$ cfu/ml of specified strains of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans* and *Aspergillus niger*. The reduction in bacteria must be log $1.0$ by day 7 and log $3.0$ by day 14 with no increase in survivors by day 28. The test for fungi does not specify a reduction; rather there should be no increase in survivors from day 0.

These less testing standards for eye drop preservatives have led to use of a wider range of preservatives in ophthalmic products in the US than in Europe.

A third test, BS EN ISO 14730, now encompassed in the British Standard for contact lens care products has been designed to determine discard dates for these products, including lubricant solutions, which have historically been used to wet and aid the comfort of contact lenses. This standard’s preservative effectiveness test involves an inoculation of at least a 10ml sample of the product with the same bacteria and fungi as used in the USP test to give a concentration of $10^5$ to $10^6$ cfu/ml organisms on day 0 and a second inoculation to give concentrations of $10^4$ to $10^5$ cfu/ml of the same organisms at two weeks. The reduction in bacteria must be log $3.0$ by day 14 and, after reinoculation at this time, by log $3.0$ by day 28. For fungi, there must be no increase in survivors at day 14 and no increase in survivors after rechallenge at day 28. Compliance with these criteria allows the allocation of a 28-day in-use shelf life.

The required reduction in cfu/ml for bacteria and fungi for the different tests is compared in Panel 3.

The vast majority of eye drops classed as medicines in the UK contain the preservative benzalkonium chloride or a combination of benzalkonium chloride and adjuncts such as disodium edetate, borax or boric acid. Charnock tested a range of artificial tears containing Purite did meet the B criteria for *Candida albicans* and *Staphylococcus aureus*. The eye drop containing Purite did meet the B criteria for both bacteria and fungal contaminants.

Although the eye drop containing Purite 0.005 per cent was free of *Candida albicans* at seven and 28 days, thus meeting the A criteria for that potential contaminant, it failed to meet the A criteria for *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The eye drop containing Purite did meet the B criteria for both bacteria, being free of these organisms at 24 hours after inoculation. The preservatives used in the other eye drop devices listed in Panel 1 were not included in this study and preservative efficacy against two of the organisms usually included in the PhEur test, 

### Panel 3: Comparison of preservative efficacy tests for eye drops

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</thead>
<tbody>
<tr>
<td>6h</td>
<td>Log 3 reduction</td>
<td>Log 2 reduction</td>
<td>Log 1 reduction</td>
<td>No increase from day 0</td>
</tr>
<tr>
<td>24h</td>
<td></td>
<td>Log 3 reduction</td>
<td>Log 1 reduction</td>
<td>No increase from day 0</td>
</tr>
<tr>
<td>7 days</td>
<td>Log 2 reduction</td>
<td>Log 2 reduction</td>
<td>Log 3 reduction</td>
<td>Log 3 reduction</td>
</tr>
<tr>
<td>14 days</td>
<td>Log 1 reduction</td>
<td>Log 1 reduction</td>
<td>Log 3 reduction</td>
<td>No increase from day 0</td>
</tr>
<tr>
<td>21 days</td>
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<td>No increase from count at 24h</td>
<td>No increase from count at 14 days</td>
<td>Log 3 reduction</td>
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<td>28 days</td>
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<td>No increase from count at 24h</td>
<td>No increase from count at 14 days</td>
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Panel 4: Comparison of ophthalmic preparations, contact lens care products and artificial tears

<table>
<thead>
<tr>
<th>Ophthalmic preparations</th>
<th>Contact lens care products</th>
<th>Artificial tears</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typically used for short periods (there are exceptions, eg, glaucoma, dry eye)</td>
<td>Used with contact lenses on a long term basis</td>
<td>May be used for for short or long periods</td>
</tr>
<tr>
<td>Packaged in small volume containers (up to 15ml)</td>
<td>Distributed in larger volume containers</td>
<td>Packaged in small volume containers (up to 15ml)</td>
</tr>
<tr>
<td>Used on compromised eyes</td>
<td>Used with contact lenses in healthy eyes</td>
<td>May be used on compromised eyes (eg, following surgery)</td>
</tr>
<tr>
<td>Used once daily or more frequently</td>
<td>Typically used once daily</td>
<td>Used once daily or more frequently</td>
</tr>
</tbody>
</table>

Preservatives in four artificial tears available in the US were compared by Rosenthal et al., who tested Systane Free, Genten, Refresh Tears and Soothe Emollient eye drops against the preservative effectiveness tests of the USP. Refresh Tears lubricant eye drop, which contain Purite 0.005 per cent, complied with both the USP and PhEur tests for preservative effectiveness. For fungi and for bacteria, the preservatives used in the other eye drop devices listed in Panel 1 were not included in this study.27

Can UK pharmacists be reassured by the fact that the brand of artificial tears containing Purite 0.005 per cent complied with pharmacopoeial tests for preservative efficacy? The USP test is less stringent than that in the PhEur and compliance with the PhEur test for fungi and for bacteria. The preservatives used in the other eye drop devices listed in Panel 1 were not included in this study.27

Karasgianz et al determined the antimicrobial preservative effectiveness of Oxyd in accordance with the methodology of the USP.26 The ophthalmic tear solution tested contained both the USP and PhEur tests for preservative effectiveness against bacteria and fungi but the formulation of the solution tested is not specified and the relevance of this study to the product Oxyd marketed in the UK is not known.

The new “disappearing” preservatives have been introduced because of the adverse effect profile of commonly used eye drop preservatives. López Bernad et al found Polyquad and thimerosal (=thiomersal) less toxic to the corneal epithelium than benzalkonium chloride and Polyquaternium-1 and found that even high doses of Polyquaternium-1 were much less toxic than benzalkonium chloride.

The lower toxicity of these preservatives may be a valid reason for accepting their lower preservative efficacy in the PhEur test, a test in which a 28-day shelf life is to be allocated, but is this preservative efficacy valid for an extended in-use shelf life? If a manufacturer wants to validate a disc date longer than 28 days, annexes to the standard BS EN ISO 14730 annotated “informative” describe tests to determine expiry dates using a variety of methods. For example, one of the prescribable eye drop devices allocated a six-month in-use shelf life is tested against disc date procedure I in which the product is rechallenged with an inoculation of 103 test organisms at 25, 50, 75 and 100 per cent of the proposed disc date and at 14 days after the proposed disc date (personal communication).

Although this appears to be a fairly stringent test and one which reflects the “real life” situation of contamination in use compared with the pharmacopoeial test, which only confirms rapid destruction of contaminating organisms inoculated at the start of the in-use period, is this efficacy suitable for an artificial tear device when it would not be applicable to an artificial tear medicine? Other companies may use other “informative” disc date procedures.

Discard date procedure II includes a section relating to simulated use in which a 1ml aliquot is dispensed every three days for three months, a scenario which does not simulate use as an artificial tear drop that, when used for the treatment of dry eye disease, would be used much more frequently. Pharmacists cannot always determine whether the discard date procedure applied to a product is applicable to the use of the product in practice because the part IX application process is “commercial in confidence”. If a manufacturer wants to validate an artificial tear drops classed as devices must comply, BS EN ISO 14730, clearly states which eye preparations it is intended to cover: “There are differences between ophthalmic preparations and contact lens care products and some of these are significant in relation to preservative efficacy testing. Typically, ophthalmic preparations are packaged in small-volume containers and are for use for short periods on compromised eyes. Contact lens care products are distributed in larger volume containers and are used with contact lenses on a long-term basis on healthy eyes. The potential risks for contact lens care products are the solution/lens interaction causing ocular irritation and the risks of the solution contamination by the repeated (daily) use of the product.

Are artificial tear eye drops ophthalmic preparations or contact lens care preparations? This question is addressed in Panel 4.

Conclusion

In conclusion, what do we have in these new eye drop devices included in the Drug Tariff?

- A range of preservative-free, single dose eye drops that are safe to use as long as they are used as single doses
- A range of multidose, preservative-free eye drops that appear to be safe to use as long as the patient does not contaminate the dropper tip in use
- A preserved eye drop gel that is similar in composition to licensed medicinal products and, like medicinal products, should be discarded four weeks after opening
- A range of multidose, preserved eye drops, preserved with widely differing concentrations of new preservatives not used in medicinal products or a preservative frequently used in contact lens solutions, with in-use shelf lives ranging from 28 days to six months

An introduction to Part IX of the Drug Tariff states: “NHS Prescription Services will normally consider all products which carry a CE marking to be safe and of an acceptable quality.” However, on the limited published data, pharmacists do not know whether the multidose, preserved artificial tear eye drops classed as devices meet the standards required for an in-use shelf life of four weeks let alone one in excess of that allocated to those classed as medicines.

Dry eye is a complex medical condition defined as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. These eye drops, while complying with the stipulation that “prescribed items allowable on FP10 should be for the treatment of a medical condition”, are tested against a standard for preservative efficacy for contact lens care products rather than ophthalmic preparations, a standard not designed to be applied to prescribable artificial tear eye drops.

Pharmacists will not have forgotten the withdrawal of several contact lens care products in the past few years. Bausch & Lomb’s ReNu with MoustureLoc was withdrawn in May 2006 because it was linked to an increase

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requiring an ophthalmic preparation, eg, an
used for periods exceeding four weeks in pa-
ing less stringent as time goes on.
in multidose ophthalmic preparations are be-
ing products are efficacious in preserving the
preservatives other than those used in medic-
How can we be sure that eye drops using
drops (a product not marketed in the UK)
its use. These withdrawals have not been con-
fined to contact lens cleaning and storing sol-
lutions. In December 2006, Alcon recalled
also in line with the global goal of reducing environmental exposure to mercury.
artificial tear used at a therapeutic dose rather
than for daily wetting of a contact lens. In
Dec 2009 the European Medicines Agency reported on discussions by
the Committee for Medicinal Products for Human Use (CHMP) on antimicrobial preservatives in ophthalmic products for human use. A CHMP ad-hoc group of experts came to several conclusions (Panel 5).

Panel 5: CHMP conclusions

- Ophthalmic preparations without preservatives are needed for those patients who do not tolerate eye drops with preservatives. For long-term treatment, formulations without preservatives are considered to be valuable alternatives. Ophthalmic preparations without preservatives are strongly recommended for use in paediatric patients. Therefore, pharmaceutical companies should develop preparations without preservatives wherever possible in order to cater for the diversity of patients’ needs. Nevertheless, based on a review of available safety evidence, a general recommendation not to use preservatives in eye drops cannot be supported. When preservatives are required, the concentration should be at the minimum level consistent with satisfactory antimicrobial function in each individual preparation and a thorough justification for the choice of the preservative should be provided. Non-clinical and clinical studies of appropriate design and duration are needed to give reassurance that the proposed formulations are optimal in terms of benefit/risk balance. When preservatives are required, the CHMP considers that it would be prudent to promote new ophthalmic preparations without any mercury-containing preservatives, eg, thiomersal. This advice is also in line with the global goal of reducing environmental exposure to mercury.

Although fully supporting the search for less toxic preservatives for patients requiring artificial tears, ophthalmic pharmacists are concerned that efficacy tests for preservatives in multidose ophthalmic preparations are be-
increasing less stringent as time goes on.

Pharmacists require further guidance before
the use of these eye drops being used for periods exceeding four weeks in pa-
tients with a medical condition, eg, dry eye, requiring an ophthalmic preparation, eg, an
artificial tear used at a therapeutic dose rather

References

11. Spectrum The ABAB. Available at: www.spectrum-thia.co.uk/apps/content/NMTL/ ViewContent.aspx?id=27 (accessed 14 May 2010).