European Journal of Parenteral & Pharmaceutical Sciences 2007; **12**(4): 103-108

Microbiological contamination of eyedrops. Part 1: Review of the literature

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Commercial, topical, ophthalmic products ("eyedrops") are prepared and manufactured under accepted pharmaceutical standards in plastic, squeezable, unit-dose or multiple-dose containers. Eyedrops are delivered to the consumer as sterile, sealed products guaranteed to be sterile until the container is opened and used. Often, multiple-dose eyedrops contain antimicrobial preservatives to minimise contamination of the product during use. Standard *in vitro* efficacy tests measure the activity of these antimicrobial preservative systems in eyedrops. In these tests, fairly high, unrealistic, levels of micro-organisms are used to challenge the product. Even this antimicrobial preservative barrier system does not necessarily prevent microbial contamination when these products are misused after opening by patients or practitioners. Patient compliance to good practices of administration of their eyedrops undoubtedly provides the most important element in protecting eyedrops from contamination. Extensive review of the literature spanning three decades indicates that approximately 9.1% of used ophthalmic products become contaminated during use. Conversely, 90% of eyedrops do not. Few of the literature studies were quantitative and most relied only on the detection of micro-organisms in used samples of eyedrops. Over the three decades of reports included in this survey, there were very few cases of grossly contaminated eyedrops that caused ocular infections. This fact tends to indicate that the current level of eyedrop contamination in the field is tolerable and not a major health hazard.

Key words: Microbiological contamination, eyedrops, in-use testing, preservatives

Introduction

Commercial, topical, ophthalmic products ("eyedrops") are prepared and manufactured under accepted pharmaceutical standards in plastic, squeezable, unit-dose or multiple-dose containers.[1-4] Eyedrops are delivered to the consumer as sterile, sealed products guaranteed to be sterile until the container is opened and used. Following pharmaceutical recommendations, multiple-dose eyedrops often contain antimicrobial preservatives that prevent or minimise the growth of micro-organisms that might contaminate the product during use by patients or practitioners. Some multiple-dose eyedrops that contain antibiotic active ingredients can be "preservative-free" or self-preserved and need not contain any classical antimicrobial preservative agent. The standard *in vitro* efficacy tests measure the activity of these antimicrobial preservative systems in eyedrops. In these tests, fairly high, unrealistic, levels of micro-organisms are used to challenge the product. Typically, microbial challenges of up to 1,000,000 colony-forming units (CFUs) per ml of product are included in such tests. Meeting these standards does not necessarily prevent microbial contamination when these products are misused after opening by patients or practitioners.[5-7] During product use or administration, the consumer can accidentally contaminate the product with environmental bacteria or fungi, or, most likely, with his own skin micro-organisms. This report surveys the ophthalmic and microbiological literature over the past three decades to determine the typical level of contamination found in topical eyedrops during patient or practitioner use.

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Microbiological contamination of ophthalmic products

It is not surprising that ophthalmic products being used by patients and practitioners in the field can and do become contaminated by micro-organisms. Various studies have evaluated eyedrop contamination during actual or simulated use. An extensive review of the literature has yielded more than 50 such studies. These investigations are summarised in **Tables 1, 2** and **3**. They include studies that occurred over a 30-year period from the 1970s to mid 2007. They involve studies from Europe, America, Africa and Asia. Even though eyedrops are used in veterinary settings, only those for human use were considered. Both preserved and non-preserved eyedrops were included in these studies. Reports of contamination of contact lens products were not included in this review. Very few references were quantitative and determined actual counts of microbial contamination found in

Table 1. Literature reports of microbiological contamination of used ophthalmic products

Akiba 1995[38]	Japan	154 bottles used by 45 outpatients	15/154	9.7%
Akiba 1996[39]	Japan	125 ophthalmic solutions from 23 eye clinics	3/125	2.4%
Akinkunmi 2006[40]	Nigeria	28 used ophthalmic preps from traditional medical practitioners	28/28	100.0%
Anders 1985[14]	Germany	148 opened samples and stored for 0-8 years	6/148	4.1%
Anderson 1982[11]	Australia	118 containers of Timolol eyedrops used by outpatients for 2 months	2/118	1.7%
Brudieu 1999[41]	France	53 vials used by internal medicine gerontology patients	19/53	35.8%
Brudieu 1999[41]	France	113 vials used by ophthalmic ward patients	20/113	17.7%
Brudieu 1999[41]	France	166 multi-dose ocular solutions used by hospital patients	39/166	23.5%
Clark 1997[42]	USA	60 samples of ophthalmic pharmaceutical and irrigating solutions from small primary care practices	7/60	11.7%
Douch 1992[43]	UK	128 BAC preserved Timolol eyedrops used for 7 days in hospital wards	10/128	7.8%
Douch 1992[43]	UK	78 BAC preserved Timolol eyedrops used for 28 days in hospital wards	12/78	15.4%
DuBois 1989[15]	UK	556 eyedrops used in 3 different locations (ward, clinic, home)	31/556	5.6%
Fazeli 2004[44]	Iran	200 eyedrops used for up to 7 days in outpatient department	100/200	50.0%
Ford 1985[13]	USA	273 eyedrops returned to an hospital pharmacy by outpatients	74/273	27.1%
Geyer 1995[20]	USA	194 bottles of topical antiglaucoma medications used by asymptomatic patients	16/194	8.2%
Guest 1990[45]	UK	34 used eyedrops (preserved)	4/34	11.8%
Guest 1990[45]	UK	52 used eyedrops (unpreserved)	17/52	32.7%
Haas 2006[27]	USA	34 bottles of VIGAMOX used for 1 week post-cataract surgery	0/34	0.0%
Harte 1978[9]	Ireland	263 eyedrops and eye ointments from a hospital pharmacy	112/263	42.6%
Hovding 1982[10]	Denmark	638 in-use multiple dose: dispensed	82/638	12.9%
Hugo 1970[8]	UK	329 bottles used for 1-18 months by patients in a hospital clinic	8/329	2.4%
Irkec 1988[46]	Turkey	15 bottles methylcellulose	0/15	0.0%
Jackson 1994[18]	Canada	46 bottles of ophthalmic diagnostic eyedrops used in clinic for 8 weeks	0/46	0.0%
Kauffmann Jokl 2007[28]	USA	123 multiple-dose ophthalmic solutions from patients in long-term care facility	10/123	8.1%
Kim 1997[47]	USA	15 spray bottles of cyclopentolate and tetracain	0/15	0.0%
Livingstone 1998[23]	UK	295 inpatient eyedrops used for 14 days in ophthalmic clinic	27/295	9.2%
Livingstone 1998[23]	UK	341 inpatient eyedrops used for 7 days in ophthalmic clinic	21/341	6.2%
Marchese 2001[48]	Italy	8 single dose medications up to 24 hours after opening	0/8	0.0%
Martin Rodriguez 1981[49]	Spain	525 commercially available eyedrops	17/525	3.2%
Mason 2005[50]	USA	74 bottles of fluoroquinolone eyedrops	0/74	0.0%
Nentwich 2007[51]	Kenya	101 multi-dose eyedrop used for 22 weeks in ophthalmic clinic	6/101	5.9%
Olson 1982[12]	Sweden	436 used ophthalmic dropper bottles from outpatient eye clinic	10/436	2.3%
Olson 1982[12]	Sweden	412 multiple-dose vials (over half were non-preserved)	2/412	0.5%
Palmberg 1994[52]	USA	12 eyedrops of fluorescein and 15 eyedrops of proparacaine used in clinic for 1 month	0/27	0.0%
Porges 2004[53]	Israel	62 bottles of topical glaucoma medications used by 27 patients	8/62	12.9%
Prabhasawat 2005[54]	Thailand	28 samples of antibiotic eyedrops used for 1 week in inpatient setting	0/28	0.0%
Qureshi 2005[25]	UK	46 PRXFLN Minim containers used either once for one patient or once for five patients	3/46	6.5%
Rahman 2006[26]	UK	95 eyedrop bottles used from 3 to 7 days in an ophthalmic clinic	8/95	8.4%
Rauz 1996[21]	UK	58 preserved eyedrops used for 4 weeks	0/58	0.0%
Raynaud 1997[22]	France	406 eyedrop vials used for 1 week in an ophthalmic department (204) and a nursing home (202)	66/406	16.3%
Schein 1992[17]	USA	156 bottles of eyedrops used by patients with non-microbial ocular surface disease	20/156	12.8%
Stevens 1992[16]	UK	143 bottles used by cataract patients (surgical)	0/143	0.0%
Stevens 1992[16]	UK	216 bottles used in hospital by outpatients	5/216	2.3%
Tamer 1994[19]	USA	166 opened ophthalmic eyedrops used in eye clinic	0/166	0.0%
Tasli 2001[55]	Turkey	43 eyedrop bottles used in eye clinic for 2 weeks	15/43	34.9%
Tasli 2001[55]	Turkey	49 unopened and sealed eyedrop bottles	5/49	10.2%
Wessels 1999[24]	USA	1485 open bottles from 18 ophthalmic offices	1/1485	0.1%
Yokoyama 2003[56]	Japan	21 bottles of unpreserved Timolol maleate used for 1 week	8/21	38.1%
Yokoyama 2003[56]	Japan	21 bottles of Timolol maleate preserved with BAC and used for 1 week	12/21	57.1%
Zembrzuska-Sadkowska 1992[57]	Poland	134 prescription medicines made by two hospital pharmacies	0/134	0.0%
			849 of 9291 =	**9.1%**

Table 2. Eyedrop contamination trends by geographic region*

Region	No. of studies reviewed	No. of samples contaminated	Total eyedrop samples analysed	Time frame	Range of contamination rates	Average level of contamination
Africa, Asia, Middle East (Australia, Japan, Israel, Kenya, Nigeria, Thailand, Turkey)	13	202	965	1988–2007	0–100%	20.9%
Europe (Denmark, England, Germany, Ireland, Italy, Poland, Scotland, Spain, Sweden, France)	25	519	5673	1970–2006	0–43%	9.1%
North America (United States, Canada)	12	128	2653	1985–2007	0–27%	4.8%
Grand totals	**50**	**849**	**9291**			**9.1%**

*Data from references in **Table 1.**

Table 3. Eyedrop contamination trends by decade*

Decade	No. of studies reviewed	No. of samples contaminated	Total eyedrop samples analysed	Time frame	Range of contamination rates	Average level of contamination
1970s						
EU	2	120	592	1970–1978	2–43%	20.2%
Total	*2*	*120*	*592*			*20.2%*
1980s						
EU	6	148	2715	1981–1989	0.5–13%	5.5%
US/Canada	1	74	273	1985	27%	27.1%
Africa, Asia, ME	2	2	133	1982–1988	0–2%	1.5%
Total	*9*	*224*	*3121*			*7.2%*
1990s						
EU	14	240	2217	1990–1999	0–36%	10.8%
US/Canada	8	44	2149	1992–1999	0–13%	2.0%
Africa, Asia, ME	2	18	279	1995–1996	2–10%	6.5%
Total	*24*	*302*	*4645*			*6.5%*
2000s						
EU	3	11	149	2001–2006	0–8%	7.4%
US/Canada	3	10	231	2005–2007	0–8%	4.3%
Africa, Asia, ME	9	182	553	2001–2007	0–100%	32.9%
Total	*15*	*203*	*933*			*21.8%*
Grand totals	**50**	**849**	**9291**			**9.1%**

*Data from references in **Table 1.**

used products. Even though some studies analysed the contamination of the container surface or eyedropper tips, this review focused only on contamination of the actual eyedrop contents themselves. In most cases, authors used the data to evaluate risks, to report abuses or to influence or change existing standards for control, or to make recommendations on product use or administration. Some of the more significant studies and their recommendations are summarised here.

Hugo[8] examined the microbial contamination of 329 bottles of ophthalmic solutions used for 1–18 months by patients attending a hospital clinic. Only eight of the 329 bottles (2.4%) were contaminated. The authors concluded that policies regarding ophthalmic solutions and usage were satisfactory as far as microbial contamination was concerned.

In 1978, Harte[9] surveyed contamination of eyedrops and ointments returned to a hospital pharmacy from the wards of a Dublin hospital. Contamination was found in a surprising 42.6% of the returned products. The authors recommended stricter adherence to the standards on the distribution and mode of use of ophthalmic preparations and a greater flexibility in the choice of antimicrobial agents when formulating multiple-dose eyedrops.

Hovding[10] performed an extensive study in Denmark on the bacterial contamination of 638 used multi-dose eyedrop bottles. Bacteria were recovered from 82 bottles (12.9%). The flora obtained by dropping and swabbing was very similar to that of the conjunctiva and skin. The authors suggested that micro-organisms isolated by dropping often originated from contaminated dropper tips. The frequency of contaminated drops did not increase with increasing duration of use of the bottles. Repeated examinations and inoculation studies indicated that the solutions were self-sterilizing. This indicated that multi-dose eyedrop bottles preserved and dispensed as in this study may be used for more than 4 weeks without

increasing the risk of significant contamination that could cause ocular infections.

Anderson[11] in Australia assessed 118 containers of timolol maleate eyedrops used by outpatients for 2 months. Two containers (1.7%) yielded contaminants that may have occurred during testing procedures. The authors concluded that limiting the volume of the ophthalmic product might be a better way to avoid microbiological contamination than restricting its use to 30 days.

Olson[12] examined contamination of sterile eyedrops used in medical practices in Sweden. Ten of 436 in-use samples (2.3%) from an outpatient eye clinic were contaminated with micro-organisms. All the contaminated samples came from the same preparation dispensed in a dropper bottle with an inserted glass dropper. Their studies showed that inexperienced persons contaminated eyedrop solutions very easily and preservation of multi-dose products is very important. The authors also recommend that patients be given careful instructions on how to handle eyedrop containers.

Ford[13] examined 273 eyedrop bottles returned to a hospital pharmacy by outpatients and showed a 27% contamination rate. Since eyedrops that contained chlorobutol or thiomersal as preservatives had a higher rate of contamination, the authors questioned the suitability of these preservatives for ophthalmic formulations.

Anders[14] evaluated the rate of microbiological contamination of ophthalmic drops using 148 samples that had been opened and stored for up to 8 years. Six of the opened bottles (4.1%) were contaminated. There appeared to be no connection between the length of storage and the level of contamination.

DuBois[15] surveyed the levels of bacterial contamination in used eyedrops in three different situations (ie, ward, clinic, home). Of the 556 eyedrops examined, 31 (5.6%) were contaminated. The authors noted a significant correlation between the degree of use and the incidence of contaminated bottles. This correlation suggested the need for unit-dose dispensing.

In 1992, Stevens[16] studied the contamination rate of 143 eyedrop bottles used by patients who had routine cataract surgery and trabeculectomy. They also examined 216 bottles used in the outpatient area of the hospital. No contamination was found in the post-operative eyedrops, but five bottles were contaminated (2.3%) from the outpatient area. On the basis of these data, the authors recommended that it was acceptable for the patient to take their post-operative drops home if the drops were used for 72 hours or less in the hospital.

Schein[17] evaluated the level of microbial contamination of 220 eyedrop products used by patients with non-infectious ocular surface disease at the Wilmer Institute in Baltimore. The interior contents of 156 eyedrops were cultured and 20 were contaminated (12.8%). The authors concluded that microbes present in a patient's conjunctivae and their used medications represent an important risk factor for microbial keratitis in patients with ocular surface disease.

In 1994, Jackson[18] evaluated 46 bottles of used mydriatics, cycloplegics and anaesthetics in a Canadian ophthalmic clinic. None of the bottle contents were contaminated. The authors recommend that multi-use diagnostic drops can be used safely for up to 8 weeks, especially if the bottle tips are wiped weekly with an alcohol swab.

A US study by Tamer[19] revealed that none of 166 opened and used eyedrops were contaminated and concluded that eyedrops can be used for up to 30 days in multiple patients. The authors emphasised the importance of writing the date of opening on eyedrop preparations so the 30-day limit could be honoured.

In 1995, Geyer *et al.*[20] evaluated the drops and bottle tips of 194 antiglaucoma medications at the Mount Sinai Hospital in New York. The drops of 16 of the 194 products were contaminated (8.2%). The authors saw contamination related to duration of use and recommended that opened topical antiglaucoma eyedrops be replaced on a periodic basis.

Rauz[21] analysed the microbial contamination of 58 preserved eyedrops used by 58 outpatients for 4 weeks. None of the samples were contaminated. The authors concluded that adhering to standards set forth by the British Pharmacopoeia Commission for in-use eyedrop expiry dates and quality of preservative has resulted in a relatively low incidence of microbial contamination of eyedrops.

Raynaud[22] in France studied microbial contamination of 406 eyedrop vials used for 1 week in either an ophthalmic department or a nursing home. Sixty-six vials were contaminated (16.3%). There was no significant difference between the vials used in the ophthalmic clinic and nursing home. Eyedrop preparations are more likely to be contaminated on the bottle tip than in the solution. Preservatives themselves are not sufficient to ensure the sterility of multi-dose eyedrops during their use.

In 1998, Livingstone *et al.*[23] studied used eyedrops from an ophthalmic clinic. Out of 295 eyedrop samples used for 14 days, 27 were contaminated (9.1%) and out of 341 eyedrop samples used for 7 days, 21 were contaminated (6.1%). The incidence of contamination was not significantly different between the 7- and 14-day samples. The authors suggest that increasing the period of use for eyedrops in hospitals from 7 to 14 days would not present a clinically significant threat to patients' health and may lead to considerable annual savings for the National Health Service.

Wessels *et al.*[24] examined 1485 opened and sometimes expired eyedrop products in 18 ophthalmology offices in California and Tennessee and found only one bottle grew out bacteria (*Micrococcus*). The authors indicated that drops in ophthalmology offices may be used and expired, but are not contaminated.

Recently, Qureshi[25] established that three out of 46 single-dose (PRXFLN Minim) eyedrops used for one to five patients were contaminated. These results, plus an analysis of contamination of the container neck, moved the authors to conclude that repeated use on multiple individuals of a product designed for single use on a single patient exposes those under medical care to unnecessary risk. The authors recommend that ophthalmologists do not use the same Minims container on subsequent patients.

A recent study in the UK by Rahman[26] evaluated 95

used eyedrop bottles from the Tennent Institute of Ophthalmology in Glasgow and found that eight were contaminated. The authors indicated that preservative-free eyedrops in multiple application containers are at risk of contamination by potentially pathogenic micro-organisms.

Certainly, the inclusion of an antibiotic in any ophthalmic formulation can only help increase the barrier to contamination of an eyedrop product. Such was the case with the Haas[27] study of 34 bottles of a moxifloxacin ophthalmic solution used for 1 week post-cataract surgery. None of the 34 used bottles were contaminated. Haas concluded that the results suggested that contamination of a self-preserved topical ophthalmic antibiotic, such as Vigamox® solution, is unlikely even after manipulation of the bottle by the patient after a 7-day course of four times daily use.

Kauffmann Jokl *et al.*[28] assessed the frequency of contamination of ophthalmic solutions in a long-term care facility. They cultured 123 used ophthalmic solutions. Ten of the 123 multiple-dose solutions were contaminated with bacteria and eyedrops containing steroids were 5.8 times more likely to be contaminated than dry eye or glaucoma medications. The authors raise the question whether single-use steroid products might be more appropriate.

Data from a total of 50 studies (**Table 1**) indicate that 849 (9.1%) of 9291 ophthalmic bottles were contaminated. The contamination frequencies from these studies fell over the entire range (0–100%), but the mean was 9.1% with a median value of 6.5%. Half of the studies were from Europe and geographically it appears that there is more of a problem with contaminated eyedrops in Africa, Asia and the Middle East than in Europe or America (**Table 2**). The trends by decade (**Table 3**) indicate that Europe and America generally improved over the years, whereas the other geographic areas seem to be worse in the more recent studies.

Discussion and recommendations

This extensive review of the literature indicated that an average of 9.1% of used ophthalmic formulations studied become contaminated during use. No manufacturer of ophthalmic products guarantees the sterility of their products after opening and it is not surprising that these products can become contaminated during use. Few of the literature studies were quantitative and most relied on the detection of organisms in used samples of eyedrops. Over the three decades of reports included in this survey, there are very few cases of grossly contaminated eyedrops that caused epidemic infections. Since cases of epidemic eye infections caused by contaminated eyedrops have been rare during this time,[29–32] the current level of product contamination in the field is probably tolerable and not a major health hazard. Even the presence of a small amount of preservative would dramatically reduce the chance of microbial contamination of eyedrop preparations. Ophthalmic products containing antibiotics could also be preservative-free or self-preserved and require no additional antimicrobial preservative agent.[33,34] Eyedrops with some preservative or antibiotic activity, but judged insufficient by official antimicrobial preservative standards,[2–4,35,36] probably have sufficient preservative efficacy to overcome normal microbial contamination in the real world. The types of preservatives used in the products reviewed here did vary and through the decades new preservatives were introduced and some were dropped. This factor also had an influence on the outcome of these studies. In-use studies that approximate the real world of contamination offer another view of the robustness of any antimicrobial preservative system in eyedrops.[37] A certain level of contamination of used eyedrops is expected and probably can be tolerated without serious consequences. Nevertheless, multiple authors cautioned care in the use of eyedrops and emphasised good patient training on appropriate use. There were also cautions on not over-using multiple-dose eyedrops in clinics on different patients. It is probable that improper usage of these eyedrops by the user was a large contributor to the contaminated products found in these studies. Patient compliance to good practices of administration of their eyedrops undoubtedly provides the most important element in protecting eyedrops from contamination.

Literature searched

Literature published from 1970 to mid 2007 was searched; search terms included product contamination, microbial contamination, ophthalmic, eyedrops, in-use, used products, preservative efficacy and antimicrobial preservative standards.

Part 2 of this article will be published in the next issue of the journal.

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