Janice Krushner
- Memorial Lecture -

Recent issues with glaucoma medication

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Good afternoon everybody and thank you very much for inviting me to speak at the meeting today. It's a great honour for me.

The issues I'd like to deal with this afternoon are discontinuations of glaucoma medicines, shortages of medicines, new products in glaucoma and generic versions of medication.

As a keen cyclist, I very much appreciate being able to cycle on discontinued railway lines, so some line discontinuations are useful but others not quite so beneficial. For example, in 2011 Pilogel®, a once daily gel applied to the eye at night was discontinued. Patients who needed pilocarpine had to change from having a once daily preparation to drops going in three or four times a day.

Then last year we saw the demise of Nyogel®, a once daily timolol gel. It had a low concentration of timolol, 0.1%, so was quite useful for certain patient groups including pregnant and breastfeeding women and it was used in patient group directions, which is where non-medical staff give out medication in accordance with an instruction previously agreed by an ophthalmologist. On its discontinuation patients had to be transferred to another once daily timolol, a twice daily timolol or the preservative-free timolol 0.1%. You can see from the prices here

Monthly costs (August 2013)	
Preservative free Timoptol 0.25%	£16.90
Preservative free Timoptol 0.5%	£19.30
Timoptol LA 0.25%	£3.12
Timoptol LA 0.5%	£3.12
Timoptol 0.25%	£3.12
Timoptol 0.5%	£3.12
Timolol 0.25%	£1.42
Timolol 0.5%	£1.45
Tiopex 0.1% Preservative free	£7.49
Nyogel 0.1% (June 2012) (Withdrawn)	£2.85

that although we might be saving money for some alternatives, we are spending quite a bit more money for others.

Coming on to drug shortages then. It all started in September 2009 when Merck Sharp and Dohme (MSD) introduced their new preservative-free prostaglandin analogue tafluprost or Saflutan®. Not long after this product was launched we started to experience shortages of other MSD products. In February 2010, only a few months after the introduction of Saflutan®, we

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started to see shortages of Timoptol® preservative-free. These shortages are ongoing. In July 2011 we started to see shortages of dorzolamide (Trusopt®) preservative-free. This is also ongoing.

We have seen Cosopt® preservative-free come and go, come again and go again. Supplies are very erratic. You will notice on this slide it says, "It is possible that there will be intermittent shortages of these products until the end of 2012". Well here we are in March 2013 and the situation remains the same, but what annoys pharmacists and ophthalmologists most I think, is that every letter we receive from the company about it, states that the supply of preservative-free Saflutan® is not affected.

On the MSD website, which was updated last month, we see that there are still shortages of Timoptol® unit dose 0.5% and 0.25% and Trusopt® unit dose 0.2%.

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***Editors Note**: This talk was delivered in March 2013; we understand the shortage of supply for Timoptol®, Trusopt® and Cosopt® preservative-free has now been resolved.*

Shortages worry patients; what is a patient supposed to do? Eleven percent of the calls to the Sightline at the IGA in July and August 2012 related to shortages of products.

Has anything good resulted from the shortages? Well the shortage of preservative-free Timoptol® meant that we had to look for an alternative and luckily, at about the time the shortages started, a new once daily preservative-free timolol, Tiopex® was introduced. Advantages are twofold, firstly it is a once a day product, secondly it is less expensive to the NHS at £7.49 for a months supply as opposed to between £17 and £19.

***Editors Note**: These prices have recently been reduced as in the chart on page 7*

Has anything good resulted from the shortage of Trusopt® or Cosopt® preservative-free? Not that I can think of. All we have is a lot of very concerned patients and worried ophthalmologists and pharmacists. However, now things might start to improve. At the beginning of 2013 we have seen the launch of two new alternative products. In January bimatoprost preservative-free, Lumigan® was introduced, and this month we've seen the launch of latanoprost preservative-free, Monopost®. Hopefully this will take the pressure off the Saflutan® and perhaps MSD can focus some of their resources on giving us back some of the other preservative-free products, Cosopt®, Dorzolamide®, and Timoptol®.

The other products that have been affected by shortages are produced by Alcon. We have had problems with brinzolamide (Azopt®); travoprost (Travatan®) and travoprost with timolol (Duotrav®). The reason these are in short supply is that they cost more in continental Europe. As a result certain greedy individuals based in the UK will make a quick profit selling them to European customers instead of these products going to UK patients. Alcon has done their best to redress the shortage created in the UK by putting up to 25,000 units per month more into the UK market than the estimated need but these shortages do continue on and off. However pharmacies with a genuine demand for an increase in supply of these products can contact Alcon direct. Has anything good resulted from this? I would say no, non and nein!

So what do we have in the way of new products? Well back in 2010, at the beginning of the year we saw the launch of a new bimatoprost (Lumigan®.) While the new eye drop is a lower

strength of bimatoprost, it contains a higher concentration of benzalkonium chloride. Unfortunately this came in at a 20% increase in cost. Although there may be benefits of this product, it has caused some confusion because some prescriptions are still hand-written rather than selected from a computer generated list. If an ophthalmologist or GP simply writes bimatoprost and doesn't specify a strength, then the pharmacist, if they can't get hold of the prescriber to check, will dispense the lower strength and that may or may not be what was intended or what the patient requires.

Other new products introduced are the new formulations of travoprost (Travatan®) and travoprost with timolol (Duotrav®). In these the preservative has been changed to one called Polyquad® and although Polyquad® had been used in contact lens solutions and also in artificial teardrops this was the first time this preservative had appeared in a medicinal eye drop. There was no change in price on introduction, but later in the year Alcon put their prices up. Why were there all these changes in such a short time?

Well, it may be that these other pharmaceutical companies were trying to gain an advantage by getting their products prescribed when they were well aware of what was coming. What was coming was the patent expiry on Pfizer's latanoprost, Xalatan®, and the launch of generic latanoprost. We already have a number of glaucoma medications available as generic products, so why has there been so much discussion about generic latanoprost in particular? Well the reason is that in the financial year 2011 to 2012 the NHS in England, England alone, spent £112 million on topical glaucoma therapy and, of that £112 million, 39% was on latanoprost, about £44 million. So, if there is such a huge market for a medication, a lot of manufacturers are going to be interested, and every Tom, Dick and Harry, will want their generic latanoprost to have a large share of that market.

As a result, in January last year when we saw the launch of generic latanoprost, bottles started to come in all shapes and sizes, which led to confusion for everybody, especially patients. In July and August last year, 15 percent of the calls to the IGA Sightline involved questions relating to generic medication. Should we be worried about the introduction of generic eye drops? Well, theoretically no.

The rules which apply to generic systemic medication are that manufacturers need to show that the new drug has the same bioavailability within the range, the rather wide range, of 80 percent to 125 percent of the original product.

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This doesn't apply to topical medications and manufacturers only need to establish products are equivalent if there is a significant change in the formulation. For example, if you have a change in the active ingredient, maybe from a soluble product to an insoluble product which means you then have a suspension rather than a solution, or you have a change in the inactive ingredients, including completely new chemicals in your formulation, or if there's some change in the application device, such as an eye spray rather than eye drops, equivalence tests must be conducted.

Well, none of this has happened with generic latanoprost.

Should we be concerned?

There are a number of questions to be asked:

- do generic versions contain the same ingredients?
- at the same concentration?
- are they equally effective?
- are the licensed indications the same?
- are they equally acceptable to patients?
- are there any other concerns we need to address?

Well, the first question – do generic versions contain the same ingredients? The answer to that is yes they do. The ingredients that I've put in red, those are the same chemical just three different names for the same chemical. Similarly in blue, that is the same chemical compound. The active drug, the preservative, some sodium chloride and water, either water for injections or purified water are present in all these formulations

Q. Do Generic Versions contain the same ingredients?

	Ingredients										
Version	Latanoprost	Benzalkonium chloride	Sodium chloride	Sodium dihydrogen phosphate monohydrate	Sodium dihydrogen phosphate dihydrate	Monobasic sodium phosphate	Anhydrous disodium dodecahydrate	Disodium phosphate dodecahydrate	Water for injections	Purified Water	Sodium hydroxide or hydrochloric acid for adjusting the pH
Xalatan											
Pfizer Limited											
Winthrop Pharmaceuticals UK Ltd											
Beacon Pharmaceuticals Ltd											
Actavis Group PTC ehf.											
Sandoz Ltd											
Arrow Generics Ltd											
Tubilux Pharma S.p.A											
TEVA UK Ltd											
PH&T S.p.A											

A. Yes

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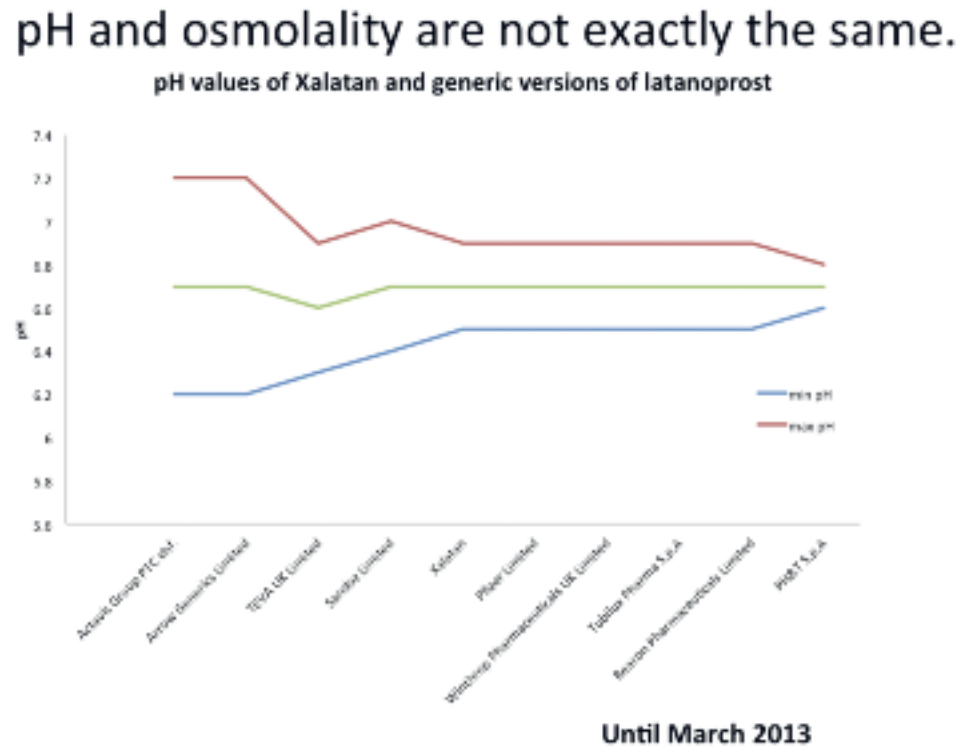
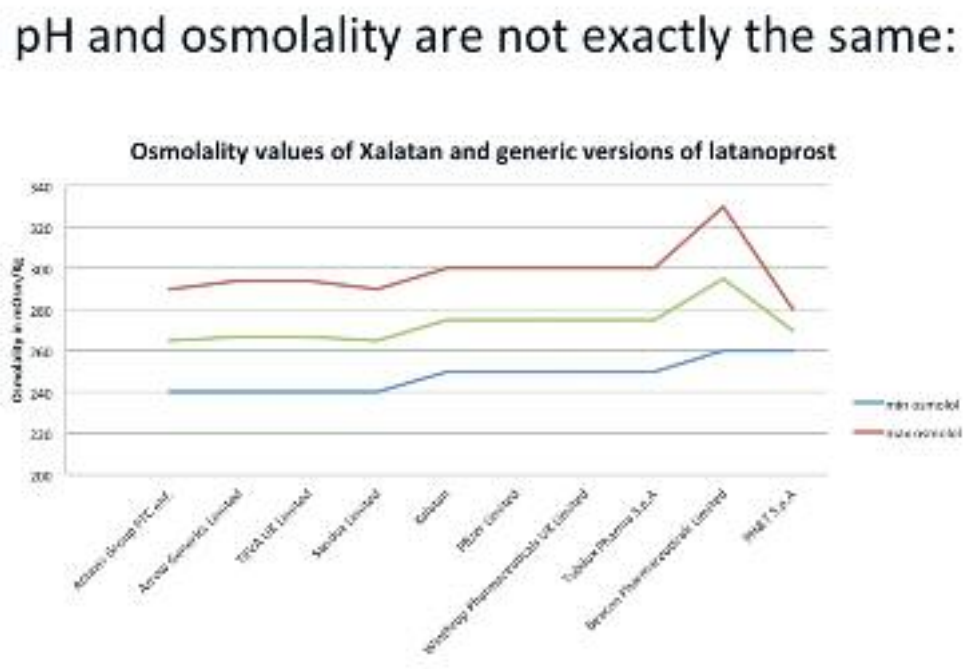
and additionally something to adjust the pH in one of these drops.

So generic versions contain the same ingredients but do they include them at the same concentration? Yes, for the active ingredient latanoprost and the preservative benzalkonium chloride. For the other ingredients we don't know because the companies keep that information to themselves, but if they alter it too much, then they would have to do studies to make sure it was equally effective. So we can look at the pH, the acidity or the alkalinity, of the product and see they're all fairly similar, although some have a wider range of pH values, the middle of the range is either 6.6 or 6.7. So all much the same. That's until this month, but I'll come on to that later.





The osmolality is a measure of how strong the solution is and patients with particularly sensitive eyes might detect a slight difference depending on the actual content of chemicals in the bottle. Again, this is much the same,

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Photograph courtesy of Jane Mottershead, Manchester

perhaps a bit more variation than pH. You can see Xalatan® there in the middle and some other formulations look exactly the same.

Are they equally effective? There haven't been very many studies on this, but the ones that have been published, one in the European Journal of Ophthalmology last year and one that has appeared on line but yet to be published in hard copy say yes, they are. The other thing I looked at was a comparison of the number of reports of 'drug ineffective' received by the Medicines and Health care products Regulatory Agency (MHRA) before and after the generic latanoprosts were launched. In the eight months following the launch of generic latanoprost, the MHRA received two adverse drug reaction reports classified as 'drug ineffective'. These reports could have related to a generic latanoprost or they could have referred to Xalatan®. The year before there had been one report about Xalatan® not being effective, so statistically we wouldn't call that a huge difference.

Are the licensed indications the same? This is probably not of great concern to our adult patients, but maybe it is to paediatric patients or their parents. Only three generic versions are licensed for paediatric use in addition to Xalatan®, so, in my hospital we keep one of these brands, because being licensed for paediatric use, parents will not worry that this drug is not suitable for use in their children.

The bigger question is 'are they equally acceptable to patients?' and the answer to that I think, is not necessarily. The patient may notice a slight difference in pH or osmolality. They might not find it tolerable. Can they open the bottle? Can they administer the drops as easily as they did before and is there anything which will stop them remembering to use their drops? We have seen that when generic brimonidine arrived these bottles came in all shapes and sizes and putting them in a certain compliance aid worked for the original product but not so well for a generic. That extended dropper tip in the picture overleaf would have ended up on the patient's cheek.

Generic latanoprost as we've seen comes in all shapes and sizes. So, when we come to opening the bottle what will the patient have been using? Xalatan® may be opened with the help of a Xalatan® bottle cap opener so what will patients be using in the future? For many of the generic bottles the Xalatan® bottle opener is too small – a new opening aid will need to be provided for patients who have difficulty opening the bottle. The next consideration is the positioning and squeezing of the bottle. The patient may have been using a Xalease® or an Opticare® compliance aid fitted with the collar for Xalatan®. Patients may have to investigate other compliance aids, helped by their ophthalmologist, their nurse in the glaucoma clinic, their pharmacist or the IGA.

Although I have tried to prepare a table of compatibility of compliance aids with the range of generic latanoprosts, I was unable to obtain samples from all manufacturers so it is incomplete. However, for every version I've seen there is a compliance aid that is compatible; it's just a matter of finding one which is suitable for the drops being used by an individual patient. Unfortunately as we know, the generic drops you're given one month might be different from the generic drops that you were given the previous month as the pharmacist may dispense a generic from a different manufacturer.

Finally, will a patient remember to use their drops? When the generic versions were launched Xalatan® and eight of the generics stated 'Store in the refrigerator, but after first opening the bottle do not store above 25 degrees and use within four weeks'. So a patient does not have to keep their generic latanoprost or their Xalatan® in the fridge for the four weeks they have it in use. However, one generic, manufactured by Teva, said 'Store in a refrigerator'. The instructions made no mention at all about use out of the fridge. That was inconvenient for a lot of patients. If you go up the stairs to bed and your eye drops are in the fridge downstairs, that's a problem.

However, so many pharmacists phoned Teva, as I'm sure staff at the IGA and

many patients did, to say 'what's all this about?' and Teva changed their instructions. The issue was resolved in October 2012, when they said 'No, it's okay for four weeks at room temperature'. So that problem has been resolved. I identified a lot of these potential problems and brought them to the attention of my profession when I published an article in the Pharmaceutical Journal last year aiming to help pharmacists to help their patients[1].

Now for something else which may interest you. In primary care in England alone, so that's not including Scotland, Wales or the hospital sector, Pfizer who make Xalatan® had being selling three and a half million latanoprost, as Xalatan®, a year. That's worth nearly £44million. They could foresee that the sales of Xalatan® would plummet so they had to do something. What did they do? They introduced a generic latanoprost and it looks very like Xalatan®. In fact it was exactly the same as Xalatan® only it hasn't got an 'X' on the label. The contents were identical; the bottle is identical.

The other thing they did was to make deals with large users of latanoprost. Just as you might be able to get your favourite brand of coffee from a big supermarket chain but not from Lidl, the big buyers could afford to make a deal. I visited the eight pharmacies in my home town in Warwickshire to determine who was stocking what in the way of latanoprost. Four of these pharmacies stock generic versions of latanoprost, so you go one month and you get one product, you go the next month you might get a different product, but one pharmacy stocks only the Pfizer generic and three pharmacies stock only Xalatan®. They have a purchasing agreement with Pfizer. This means that if you have a prescription for latanoprost you might get a generic but if you go to certain pharmacies you could get Xalatan®, so if you preferred your old Xalatan® then you needed to seek out a pharmacy that stocked it and stick with them.

Has anything good resulted from latanoprost going generic? Well it's a cost issue; the price of latanoprost in January 2012 was £12.48, in March 2013 it is £3.22. Recently we have seen annual savings to the NHS of £32.4million.

[1] Titcomb, L *The Pharmaceutical Journal*; 2012. Vol. 288, P. 709

***Editors Note**:The latest price of generic latanoprost is £2.22*

Just as 'you thought it was safe to go back into the water' something else has happened. The original patented Xalatan® has changed. Pfizer has changed the concentration of one of the ingredients, the phoshate buffer. This allows room temperature storage but reduces the shelf life of the product

from three years to two years. This change will alter the pH and the osmolality, properties which we've already talked about. The new formulation is presented in new packaging no longer with the yellow flash on it, but with a green flash. This change only applies to Xalatan®, not the Pfizer generic which remains the same as the original Xalatan®, or to Pfizer's latanoprost with timolol, Xalacom®. What will this change mean to patients? Not an awful lot because when they were given their original patented drops they knew that when the bottle was opened they could store it at room temperature anyway but the pH value of Xalatan® has fallen from 6.7 to 6. Which product is out on a limb now?

So has there been any silver linings to all these issues in glaucoma medication? The reviews of medication necessitated by discontinuations may have benefited some patients; shortages have stimulated the take up of new products. These new products may be preferred for some patients; generic versions of patent loss products may suit others. Certainly, there has been an increased level of competition in the market and great cost savings to the NHS when the NHS really does need it. The new formulation of Xalatan®?

It's only been available for a fortnight so time will tell.

Open Question and Answer Session:

Keith Martin: I was surprised when David Wright sent me an article from the G.P. News, or something like that a few weeks ago saying 'Generics available! Great news for the NHS!' There's absolutely no mention of anything except price. And that's typical of the NHS brainwashing system in my view, sorry for any negativity, but that's the way they do things. I think you've highlighted a huge number of issues that we have whilst we don't really want to be completely led by the pharmaceutical industry on this either, there are other issues other than just price.

Q. Two questions about Minims®. One is that it says use once and throw away and I was told by the dispensing pharmacist at the hospital "No, no, you can use it – keep it for a whole day. You can ignore what they say on the box". And the other thing about Minims® is, I can manage it but I can imagine in ten years time I won't. I find they require, compared to my other eye drops, an incredible amount of force to actually press them in. So, no problem now but as it's going to be a problem, thank you.

A. Yes indeed. Minims® are a problem because Bausch & Lomb have the monopoly on unit dose eye drop manufacturing. There are other unit dose eye drops as we've seen; when

you can get hold of them! MSD do some but the Minims® range is the largest range available, and they are incredibly difficult to squeeze. I was lecturing to nurses yesterday and one of the questions that came up was – "Is there an alternative to this, because it takes so much pressure to squeeze these things, and we're doing it day in day out, nursing staff get repetitive strain injury by squeezing Minims®". We are certainly aware of the problem. The reason the Minims® are so hard I understand, is that the plastic has to withstand sterilisation because, unlike other unit dose eye drops, the Minims® are sterile on the outside as well as on the inside of the unit. They are designed in this way so in the operating theatre they can be opened up and put onto a sterile field and a surgeon or a nurse assisting can pick it up knowing the outside of the product is sterile. I have suggested to the manufacturers that they ought to have two ranges - an outside of theatre range and an inside theatre range because the majority of Minims® eye drops are not used in theatre and we would very much like a softer plastic. Can we use them on more than one occasion? The official answer is "No". The product licence says 'Use once and discard'. That is what we say in my hospital, but I know advice varies from hospital to hospital.

Keith Barton: All these safety issues are such a hot topic. Nowadays we have to be a bit very careful about what we recommend but some of these patients have been on something eight times a day and we used to say use one a day and then throw it away, but the official line will always be use according to the product licence which is use once and throw away. Unfortunately this is an enormous waste but there only needs to be one patient damaged from off licence use and that would be one too many.

Q. On the theme of Minims® being very inflexible, I use Azarga® and the bottle I now have is very rigid and very difficult to use. I wondered if you could bring your best endeavours on other manufacturers of some of the bottles too, please?

A. Most certainly. I don't think they test these enough on patients. Getting patients to assess the delivery device is so important in all medicines from inhalers to eye drops.

Q. After what you've said I don't think I understand generic. Is there a definition of generic and isn't there something to do with the Trade Descriptions Act and can't it be made in such a way that the generic is the same as the original?

A. Not absolutely because the manufacturer of the new generic product will not be able to get hold of the exact formulation of the original

patented product, anymore than I could. That's confidential information to Pfizer for example, with respect to Xalatan®, and they are very unlikely to want to give out the exact formulation. More could be done to improve the delivery systems but manufacturers may choose a cheap container because they want to maximise their profits. There are some containers amongst the generic latanoprost that are better than others, no doubt about it.

Q. Where does Iopidine® come within the various eye drops which you've been talking about?

A. Iopidine® is still classed as a branded drug. It's probably not a large enough market to make it worth people manufacturing a generic. It was featured on my slide but represents a tiny percentage of all the glaucoma medication dispensed.

Q. Is it the case Lucy that we don't know the long term effects of preservatives in eye drops?

A. The conjunctival and corneal surfaces can become damaged from preservatives, so we do try to restrict the amount of preservative put into the eye and as a general rule, if you're using six drops per day or more of eye drops, then the ophthalmologist starts thinking preservative-free. If you have pre-existing corneal damage, for whatever reason, then preservatives should be avoided altogether. However, there are a number of ways of reducing what we call 'the preservative load'. If you need two different drugs, for example, then giving a combination product, that is two drugs combined in the one bottle, will only contain one quantity of preservative. So there are a number of ways we can look at minimising the amount of preservative the patient's eyes receive. I understand that in glaucoma, if you use an awful lot of preservative-containing drops on the eye, surgery is not always as successful compared with using preservative-free eye drops. Surgeons can try to damp down the inflammatory response from preservatives just before surgery; I've seen that done as well. Maybe the ophthalmologists would be better to comment on that.

Q. Would it be a simplistic question on the part of a patient who doesn't know about the details of the effectiveness of medication to say 'I would like to have preservative-free, because preservative-free sound better'?

A. There are an awful lot of ophthalmologists who would say that in an ideal world all eye drops would be preservative-free and we would not subject patients' eyes to any preservatives. There has also been some European guidance to say that long-term conditions should be treated

Q&A

with preservative-free eye drops but the cost in comparison to bottles of eye drops is astronomical.

Q. In this country twenty eight days is the maximum usage for a bottle. In other countries they get larger volumes and they can use them for longer, why?

A. Back in the sixties eye drops became contaminated with a really nasty bacterial organism called Pseudomonas that can damage eyes very badly and there were even problems with loss of eyes. Following these incidents, the powers that be said "right we can't just have a free for all on these eye drops, we need to decide upon an 'in use' period after opening" and, as you say in this country it's twenty-eight days. It's a figure that was plucked out of the air really, there's no evidence that after twenty-nine days or thirty days you can't use the drops and I would always say, if the twenty-eight days is exceeded by a couple of days, don't stop using the drops. You do more harm by stopping using the drops than you would by carrying on using a bottle for a few more days until you can get your new supply. There have been studies showing contamination of eye drop bottles in various scenarios but there are so many different factors to suggest definitive guidelines about what should happen, so we're stuck with twenty-eight days in this country.

Q. Just on the back of that previous question. I have my prescription changed quite regularly. Is there any way that we can return and recycle for use, any unopened bottles that have been issued through the pharmacy rather than just throwing them away which seems a terrible waste to me?

A. It does seem an awful waste but I think the answer to that is not issuing patients with so many drops on one prescription. At the surgery where I work we issue a month's supply at a time and that is very much encouraged because issue of greater quantities results in the wastage which you describe. There is a huge amount of medicines wastage. There are triple packs of certain glaucoma therapies but if a patient is just about to go to the hospital to be reviewed then issuing them with two, three or six month's worth of a treatment that is not going to be used is incredibly wasteful.

Thanks very much indeed.

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