In certain ocular pathologies, ophthalmic formulations need to be chronically administered in order to guarantee their efficacy. Typical examples of such pathologies are dry eye and glaucoma. Nevertheless, although preservatives have been frequently used in eye drops, its frequent use has been associated with alterations in the precorneal film, while in patients suffering from dry eye they tend to aggravate the already existing problem. On the other hand, in glaucoma patients the prolonged use of eye drops with preservatives has been associated with changes in the ocular surface accompanied by inflammation. In fact, conjunctival biopsies in patients suffering from glaucoma have revealed an increased number of immune cells and fibroblasts (1,2).

Thanks to the experience garnered so far, we can say that the successive administration of formulations with preservatives has a toxic effect in the ocular surface and in particular in those patients whose surface is compromised. However, as stated by the Real Farmacopea Española (RFE), the use of preservatives is mandatory in the case of multidose formulations, since bacterial contamination takes place when handling containers twice a day for two weeks. As quoted by the RFE (3): *Aqueous formulations in multidose containers shall include the appropriate antimicrobial preservative at adequate concentrations in order to prevent tampering of preparations during the time of use, except in those instances when preparations feature sufficient antimicrobial properties.*

A wide number of preservatives is used in the formulation of eye drops, among them benzalkonium chloride, benzethonium chloride and cetyl pyridinium chloride, benzyl bromide, EDTA, phenylmercury nitrate, phenylmercury acetate, thimerosal, merthiolate, acetate and phenylmercury borate, polymyxin B sulphate, chlorhexidine, methyl and propyl parabens, phenylethyl alcohol, quaternary ammonium chloride, sodium benzoate, sodium propionate and sorbic acid.

Progress in the treatment of dry eye has been linked to the emergence of new preservatives in the market based on stabilized chloride and oxygen compounds (Purite®) as well as sodium perborate (4). These agents have raised enormous interest since they were effective and apparently did not entail epithelial damage as other conventional drugs did. In any case, one of the most significant advances in the treatment of dry eye was the development of preservative-free artificial tears in monodose containers or else the inclusion of a sterilizing filter in multidose containers (Sistema Abak®).

The action mechanism of preservatives may be divided into two main categories: surfactants and oxidants (1,2).

Surfactants act upon microorganisms altering the cellular membrane and resulting in the lysis of the cytoplasm content. Cells in mammals cannot neutralize chemical preservatives, and thus preservatives become part of the cell and results in toxic effects. The classical example for this type of agents is benzalkonium chloride.

Oxidizing preservatives are usually smaller molecules interfering with cell functions. They may destabilize membranes, although to a lesser extent than chemical agents may. They are less toxic for mammal cells, which are equipped with enzymes capable of catalyzing the decomposition of hydrogen peroxide as long as preservatives are found in
low concentrations. Stabilized chlorine and oxygen compounds and sodium perborate are some examples of oxidizing preservatives.

Taking into account their impact on the corneal epithelium, it is clear that preservatives should not be used when there is some kind of trauma or in patients who have undergone a surgical procedure, since there is a risk of causing irritation in the anterior chamber. We need to take into consideration the fact that these agents are exclusively devoted to preventing the potential contamination of solutions by microorganisms during the use of this medication and should not to be included in formulations for intraocular use.

Another relevant aspect to take into account is that the intermittent use of formulations with preservatives needs not to be theoretically linked to adverse side effects. However, the use of several eye drops at the same time increases exposure to preservatives, since the concentration to which the ocular surface is exposed increases together with the number of applications. Furthermore, repeated doses may result in the accumulation of preservatives.

Obviously, the use of preservatives in ophthalmic formulations is necessary and cannot be avoided. Nevertheless, we should determine which preservatives induce less toxicity in epithelial and conjunctival cells. Cellular lines and cellular feasibility trials are efficient tools to bring about these studies.

REFERENCES