Nemera

USING INTELLIGENT DESIGN TO **DELIVER** SAFE PRESERVATIVE-FREE MULTI-DOSE EYE DROPS

A significant patient population requires the long-term use of eye drops multiple times a day. Maintaining the sterility of eye drops is important for patient health. Single-use doses are expensive and preservatives can cause allergies and irritation but, as Ms Fanny Sellier, Global Category Manager, Ophthalmic, Nemera, explains here, the intelligent design of multi-dose bottles provides a viable means of delivering safe, preservative-free eye drops.

PATIENTS NEED STERILE EYE DROPS

A large number of patients have conditions that require the long-term daily use of eye drops. For example, dry-eye syndrome is associated with aging, contact lens use and environmental factors such as windy and sunny weather. It affects an estimated 5% of over 50s in the US [1] and is usually managed using an artificial tear solution which needs to be applied up to four to six times a day, often for the rest of the patient's life. Conditions such as hay fever and glaucoma also require the long-term use of self-administered eye drops.

It is important that all eye drops are kept free from bacteria. The microbial contamination of eye drops is a significant risk factor in the development of bacterial keratitis.[2] Post-operative patients are at particular risk of infection, as are patients who have used topical steroids, since these lower the ocular defences.[3]

PRESERVATIVE-FREE BETTER FOR PATIENT HEALTH

One way of keeping multi-dose eye droppers safe for patients is to add preservatives to the formulation.

However, the use of preservatives can cause allergies or ocular irritation, and some can even cause a toxic response, damaging patients' eyes.[4] Any such reactions is a particular issue for patients who rely on the long-term use of eye-drops for chronic conditions.

In 2009, the European Medical Agency stated that the "inclusion of antimicrobial preservatives or antioxidants in a finished product needs special justification". Even when preservatives are tolerated in an adult population there are still questions over tolerance for the paediatric population. The EMA has stopped short of a general recommendation not to use preservatives in eye drops, but they recommend that "preservative free formulations whenever possible should be considered" and that "ophthalmic preparations without preservatives are strongly recommended for use in paediatric patients, especially neonates".

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PRESERVATIVE-FREE UNIDOSES: EFFECTIVE BUT EXPENSIVE

Unidose eye droppers are a commonly used delivery method for preservative-free eye drops. By virtue of being single use, there is no opportunity for bacterial contamination at the point of use.

Unidoses are ideal for clinical settings, especially during surgery. However, they are too costly and inconveniently bulky to be suitable for home use in chronic conditions. Single-unit, preservative-free drops have been calculated to be 1169% more expensive to produce than the equivalent preserved eye drops in a multi-dose bottle.[5]

INTELLIGENT DESIGN FOR PRESERVATIVE-FREE MULTIDOSES

The alternative way to keep eye droppers clean is by the intelligent use of technology. Rather than relying on the anti-microbial properties of preservatives to kill any bacteria that enter the bottle, the ideal approach is to prevent any entry of bacteria into the bottle in the first place.

Multi-dose bottles dispense drops using either a non-return valve or a filtering system. Most commercially available bottles designed for multi-dose preservative free eye drops rely on a filtering system to stop the entry of bacteria. When a drop is dispensed, the volume of the dose is compensated by air. Eye drops can become contaminated in two main ways: by contaminated air entering the device or by contaminated liquid re-entering through the filter.

FILTERING OUT THE BACTERIA?

Anti-microbial filters are typically made from a nylon fibre membrane that consists of tightly packed layers of strands of nylon fibres (see Figure 1). Filters work on the mechanical principle that bacteria are large molecules that do not fit through the very small holes, while air and non-viscous solutions are able to pass through without hindrance.

Sterile 0.22 µm filters are industry standards, but their effectiveness as bacterial filters has been challenged in the literature. Unfortunately it has been found that bacteria are capable of routinely penetrating 0.22 µm filters, even when the molecules seem to be too big to fit through the holes.

In a 2002 paper, "Big bacteria pass through very small holes," Wainwright *et al* found that: "Common, potentially pathogenic, bacteria (which are nominally larger than 0.2 µm) can cross a 0.2 µm nylon membrane.[6] All of the bacteria crossed from the upper membrane surface to the solid medium below the membrane; this ability was highly repeatable and did not depend on the make of membrane used. Bacteria growing below the membrane exhibited normal size and morphology."

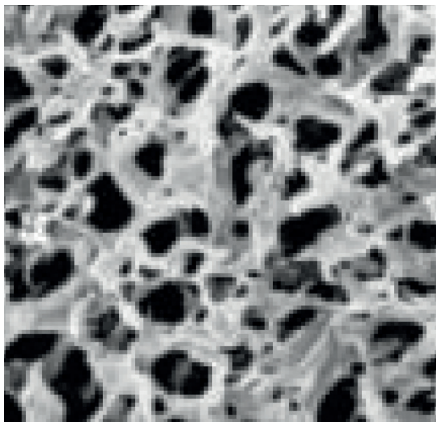

Figure 1: Scanning electron micrograph of nylon membrane filter (pore size 0.22 µm).

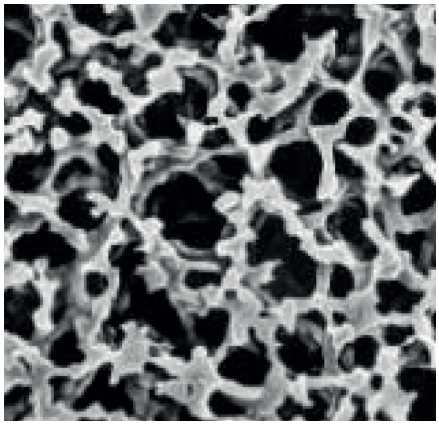

Figure 2: Scanning electron micrograph of a Millipore membrane filter (pore size 0.22 µm) showing a distribution of pore sizes.[10] (Bar in bottom right hand corner of image is 1 µm long.)

Even where filters are shown to be effective, the filtered bacteria clearly remain on the filter. A 2006 study on the efficacy of single-use bacterial filters showed "a significantly greater bacterial growth on the proximal side of the filter compared with the distal side".[7] Eye-drop filters act in two directions: pressure on the sides of the plastic bottle dispenses a dose through the filter to the patient's eye. When the pressure is released, air and a small amount of liquid passes back through the filter and into the bottle. Therefore, bacterial growth on the filter represents a contamination risk for the delivered dose.

WHAT MAKES FILTERS UNRELIABLE?

The evidence that bacteria can pass through 0.2 µm filters is clear, but the reasons are not obvious. One possibility for the observed passage of bacteria through filters could be due to the nature of the material of the filters. The sponge-like structure includes holes of varying sizes (Figure 2), some of which are statistically likely to be larger than 0.2 µm. In fact, one study found that 0.2 µm filters have a distribution of pore sizes that includes some as big as 0.5 µm.[8]

Individual testing would eliminate doubt over the viability of each filter, but the process used to test filters is destructive.[9] The testing method introduces bacteria and liquid onto the surface of the filter. This starts bacterial growth on the filter and therefore decreases the subsequent shelf life of the dispenser. Therefore, in-line testing of multi-dose dispensers that rely on filter technology is not possible. Instead, testing is carried out statistically on only a proportion of the dispensers.

However, it is likely that the presence of larger holes in the filters is not the sole mechanism of bacterial penetration. Hasegawa et al found that "*Pseudomonas aeruginosa* passed through a 0.22 µm pore size filter. The membranes which allowed passing-through of bacteria showed normal bubble point values in the integrity test". This demonstrates that bacteria are still capable of passing through a reliable 0.22 µm pore size filter.

BACTERIAL MOTILITY IS A CAUSE OF FILTER PENETRATION

Bacteria come in a variety of shapes and sizes, but many of them share the ability to self-propel by twitching, rotating or gliding. Twitching is the most common form of motility and is achieved through movement of the flagella in a way that makes the bacteria appear to swim. Studies have shown that this motility enables bacteria to move through very small channels relative to their size.

Hasegawa *et al* also experimented with a strain of *P aeruginosa* that was defective in twitching motility and found that it was unable to pass through the 0.22 µm filter. They concluded that it is the flagellum-dependent motility of *P aeruginosa* that enables it to penetrate fine filters.

BACTERIA ALSO PENETRATE BY GROWTH & DIVISION

Männik *et al* went on to find that *Escherichia coli* lose their ability to swim in channels narrower than their diameter.[13] Surprisingly, they found that despite this they are still able to penetrate narrow channels. They observed that over time, through the mechanism of growth and division, *E coli* were able to penetrate filter channels "with a width that is smaller than their diameter by a factor of approximately two. Within these channels, bacteria are considerably squeezed but they still grow and divide".

This has clear implications for the effectiveness of filters for multi-dose, preservative-free eye droppers. Filtering liquid several times a day means that the filter remains wet throughout the usable lifetime of the device, presenting ideal conditions for bacterial growth.

AN ALTERNATIVE TO FILTERS BASED ON SILICONE: NOVELIA®

A viable alternative to the use of sterile filters for multi-dose, preservative-free eye droppers is a non-return valve system used in conjunction with a silicone membrane to filter the returning air (Figure 3). The one-way valve ensures that no contaminated liquid can be re-introduced to the container after the drop has been dispensed, completely removing the need to filter the liquid. The intake of air into the dispenser takes place via a separate venting system with a silicone membrane called the PureFlow™ technology (Figure 4). The venting system filters the intake of air using a very fine membrane manufactured from silicone polymer.

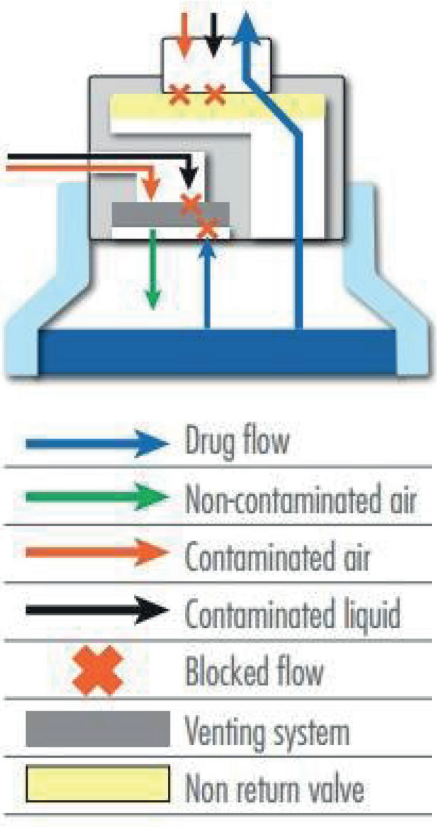

Figure 3: The Novelia® system uses a non-return valve that removes the need to filter the liquid. This makes it possible to use a silicone membrane to filter the air.

The silicone membrane is a solid, non-porous material. It is homogenous and does not contain any holes therefore its characteristics can be precisely engineered. The membrane's intermolecular distance is of the order of nanometres, allowing the passage of air through the membrane, but completely preventing the passage of any liquid or solid, including bacteria.

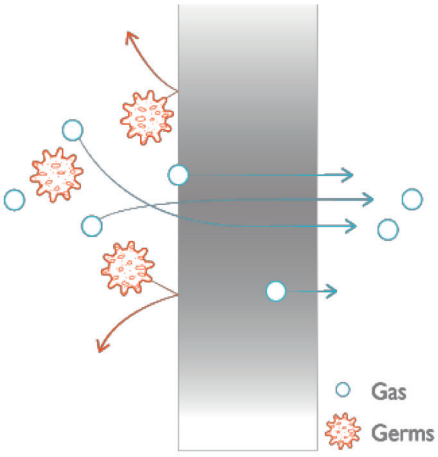

Figure 4: The PureFlow™ technology consists of using the air permeation property of the silicone to allow the air flow and avoid any bacterial penetration.

The function of the silicone membrane can be compared with an inflated balloon. The balloon is a continuous, waterproof material, yet gas slowly passes through the wall of the balloon until the pressures inside and outside reach equilibrium.

> "Devices that use this PureFlow™ technology can be tested individually in-line as a consistent part of the manufacturing process."

The separation of the dose delivery from the venting system means that the membrane is kept dry. This minimises the risk of bacterial growth on the surface of the membrane, and also means that the testing process is non-destructive. In fact, devices that use this PureFlow™ technology can be tested individually in-line as a consistent part of the manufacturing process to ensure robust quality standards. This provides an even greater assurance of safety for the patients.

SUMMARY

A non-return valve combined with a silicone membrane venting system demonstrates how intelligent design can be used to prevent the entry of bacteria into a bottle, making it possible to deliver safe, multi-dose preservative free eye drops.

NOVELIA® KEY ADVANTAGES

For the pharmaceutical company:

- 100% controlled and safe thanks to itspatented PureFlow™ technology
- Functional with suspensions and solutions up to high viscosities
- Large range of bottles
- Compatible with most existing filling lines (screw cap)
- Simplified manufacturing process thanks to preassembled cap and nozzle.

And of course for the patient:

- Preservative-free to protect the ocular surface
- User-friendly and intuitive, as easy to use as any standard eyedropper
- Blue tip for a better precision when targeting the eye
- One drop at a time in the patient's eye, calibrated drops
- Low squeeze force
- More sustainable and affordable compared to unit-dose, easier to carry.

With Novelia®, preserve patient's eyes, not drugs!

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