FANNY SELLIER, NEMERA
EYEDROPPERS DESIGNED FOR PATIENTS

Fanny Sellier is responsible for ophthalmic products at Nemera, including the preservative-free technology, Novelia®. She joined the company in 2011. A graduate from the ISEG business school in Strasbourg and the IUT de Chimie (chemical sciences) in Besançon, France, Ms Sellier worked for seven years for Rhodia (now Solvay) in the US in marketing, Lean enterprise and business development. She was then with BASF in a marketing position managing products for the home care industry.

Talking here with ONDrugDelivery Magazine, Ms Sellier discusses Nemera's multidose eyedropper system Novelia® for preservative-free formulations. She explains how this platform has been developed to improve patients' lives.

Q Thinking of all the stakeholders – patients, clinicians, pharma industry – what do you see as the most significant trends and most pressing demands driving ophthalmic drug delivery system development at present?

A I feel that one of the most significant factors driving the ophthalmic market today is adherence to treatment. There is a demand on pharma companies to provide products that are easy for patients to use with as few side effects as possible.

In particular the treatment should not irritate the patient's eyes. That's why preservative-free formulations are very useful for patients who take their treatments every day, for chronic diseases. In addition, patients need to have a product that is easy to use and that makes it simple for them to deliver the product into the eye. So a low squeeze-force is desirable, meaning that the patient does not have to squeeze the bottle too hard in order to make a drop. Also it should be easy for them to aim the drop so that it lands in the eye and does not miss. Our Novelia® platform (Figure 1) incorporates a "blue dot" which really improves the patient's ability to aim the drops accurately (Figure 2).

> "One of the most significant factors driving the ophthalmic market today is adherence to treatment."

Another aspect that I feel will be making ocular products easier to use in the very near future will be the addition of electronics into the systems. The emergence of delivery systems incorporating connectivity and electronics is very visible in the parenteral and pulmonary areas but very soon we will see electronics adopted for all types of delivery system, including ophthalmic. In fact we are working on an e-Novelia® system at Nemera – an electronic version of Novelia® which lets patients know when they need to take their drug, records whether a drop has been delivered, knows how much formulation remains in the dropper bottle and sends reminders when the patient needs to get a new bottle.

Q Please could you give a broad overview of Nemera's offering in the ocular delivery field?

A Novelia® is not just a product, it is a platform. It was one product when we first designed and developed it but we have now extended the range to provide one system that can be adapted to handle different ophthalmic formulations.

For example we have adapted the flow-control technology within Novelia® that avoids multiple drop delivery into the eye and ensures that only one drop is dispensed at a time (see Figure 3). We have three different

Figure 1: Novelia®, the only multi-dose eyedropper for preservative-free formulation registered in the UK for a Rx product.

Figure 2: Novelia® improves the patient's ability to aim the drops well.

PureFlow® versions available, each suited to formulations of different viscosities. One of the systems is for extremely liquid / non-viscous formulations (with the consistency of water), even if you squeeze really quite hard on the bottle you might get another drop but never a jet.

We also have different valves available, each one delivering a different drop size. In addition to the "standard" valve, which was the first one developed, we now have a wide range, including two smaller valves and two larger ones. The size of the drop can be customised depending on the needs of specific client products. This is particularly important for generics companies because when creating a generic version of an originator compound they are required to replicate the drop size as well as the composition of the originator product.

Additionally, we have a full range of bottles available in terms of size, material and sterilisation type. We have 5 mL, 7.5 mL, 11 mL and 15 mL bottles. For the material, all of these sizes are available in low density polyethylene (LDPE) and we're also working on polypropylene (PP). In terms of the sterilisation mode, the Novelia® bottle has been validated using both gamma and ethylene oxide (EtO) sterilisation. Offering two options for sterilisation allows us to better answer to our customers' compatibility needs.

We don't only focus on the nozzle, but also on the cap. Originally the Novelia® cap was white but we've just launched an olive green cap and we're working on other colours for specific demands. Additional cap options include a vented cap which is useful for sticky formulations, and a child-resistant cap.

> "A range of drop sizes is possible and this is particularly important for generics companies because when creating a generic version of an originator compound they are required to replicate the drop size as well as the composition of the originator product."

The objective is to enable Novelia® to be adapted to different sets of circumstances so it can be used for numerous products, not only from different clients but also different formulations within the same individual client's pipeline. That is a true platform.

Q Why did Nemera opt for preservative free with Novelia®? And why multi dose?

A Nemera chose to develop a multi-dose system for preservative free formulations because there was a real need from patients. It is about helping patients who have chronic disease avoid side effects. These patients really need preservative-free formulations.

Of course, preservative-free ophthalmic products have been available on the market for a long time. But, crucially, these were single-dose products. Unit-dose products are expensive. They're not eco-friendly either. Thinking about using unit doses over a month, that's about 30 dose units instead of one multi-dose system. There is a lot of waste when using single-dose products: waste in terms of the formulation itself; of plastic primary packaging; of secondary packaging; and in terms of storage and transportation.

Patients using unit doses could also face other issues: inconvenience of handling, difficulty of targeting the eye and risk of hurting it, caused by the long tip. The drop size is far from consistent and can vary widely depending on how the patient opens the packaging. We found that many patients around the world do not like using unit-dose products for chronic ophthalmic diseases and that's a major reason why we decided to develop a re-usable system.

Q Nemera is well known as a company with highly innovative, intelligent design capabilities applied in various areas within drug delivery. How was this expertise applied to Novelia®?

A At Nemera we always think about the patient while we're designing a product, and all throughout the development process until manufacturing. Patients are always first. We have conducted several user tests to make sure that patients understand the system and can use it easily. They always provide very useful feedback and, at the development stage, we are still able to adapt the system. So not only do we listen to their feedback but we act.

This is what happened with Novelia® at the beginning of the project. We learned from patients' feedback that is was difficult to see the drop as it emerged from the dropper. They were right. At this point the dropper valve was transparent and we realised it was important to have a

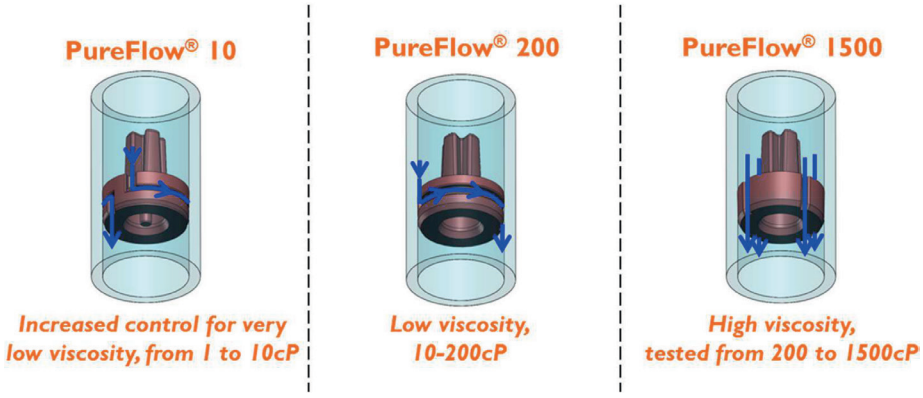

Figure 3: Three versions of PureFlow® flow-control technology adapted for different formulation viscosities.

"We received feedback from patients that is was difficult to see the drop as it emerged from the dropper. They were right. At this point the dropper valve was transparent and we realised it was important to have a contrast. So this is why we now have the blue valve – the blue tip."

contrast. This is why we now have the blue valve – the blue tip that totally contrasts with the white top part of the nozzle. This enhances the patient's view of the drop and makes it easier to aim the drop at their eye. During the development stage we're already thinking about how we'll manufacture the product. Our Innovation Center uses a quality-by-design development procedure to ensure we can manufacture the product at the highest level of quality, and to make sure we can control the quality of the product during the manufacturing.

Novelia® was initially developed with a filter technology (rather than the PureFlow® system we now use, which has a silicone membrane). However, we had to look at the evidence that it was impossible to perform full quality controls on the filter during the manufacturing process: inspecting a filter is a destructive test. As our objective was to have 100% automated control of every single product for patient safety, we decided to go for a silicone membrane instead of a filter.

Another important feature of Novelia® is its protective cap. With the Novelia® cap, patients can easily see that the bottle has never been used, thanks to its tamper-evident ring. In fact, when the patient unscrews the cap for the first time, the tamper-evident bridges break. This feature differentiates Novelia from most multi-dose eyedroppers for preservative-free formulations on the market. We see devices that allow the medication to be dispensed even when the tamper-evident ring is still in place, and others that do not even have a tamper-evident feature.

However, if microbial contamination on the tip does take place while the cap is removed, the system contains silver ions embedded in two components – the surface of the cap and on the top of the nozzle. Silver ions inhibit the growth of microbial contamination and are globally widely used in a variety of applications including pharmaceutical and medical applications such as lens cases, wound dressings and also in other eyedroppers.

The silver ions are not in permanent contact with the formulation contained in the bottle. Any leaching of silver in the delivered drop will be consequently minimal and well below any safety threshold.

Figure 4 shows the Novelia® function summarised in five steps including the function of the valve, the PureFlow® technology, which allows air to diffuse into the bottle to equalise the pressure inside and outside the bottle whilst preventing microbial ingress, and the silver ions embedded in the cap.

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Q Another strength of Nemera is its industrialisation know-how including substantial in-house manufacturing facilities. Does Novelia® take advantage of these capabilities?

A Nemera is expert in high volume manufacturing of drug delivery devices. We manufacture hundreds of millions of parenteral and pulmonary devices, on fully automated lines and in GMP conditions. We design our products from scratch with the manufacturing process in mind. This experience we have at Nemera with other types of delivery system certainly helped us develop

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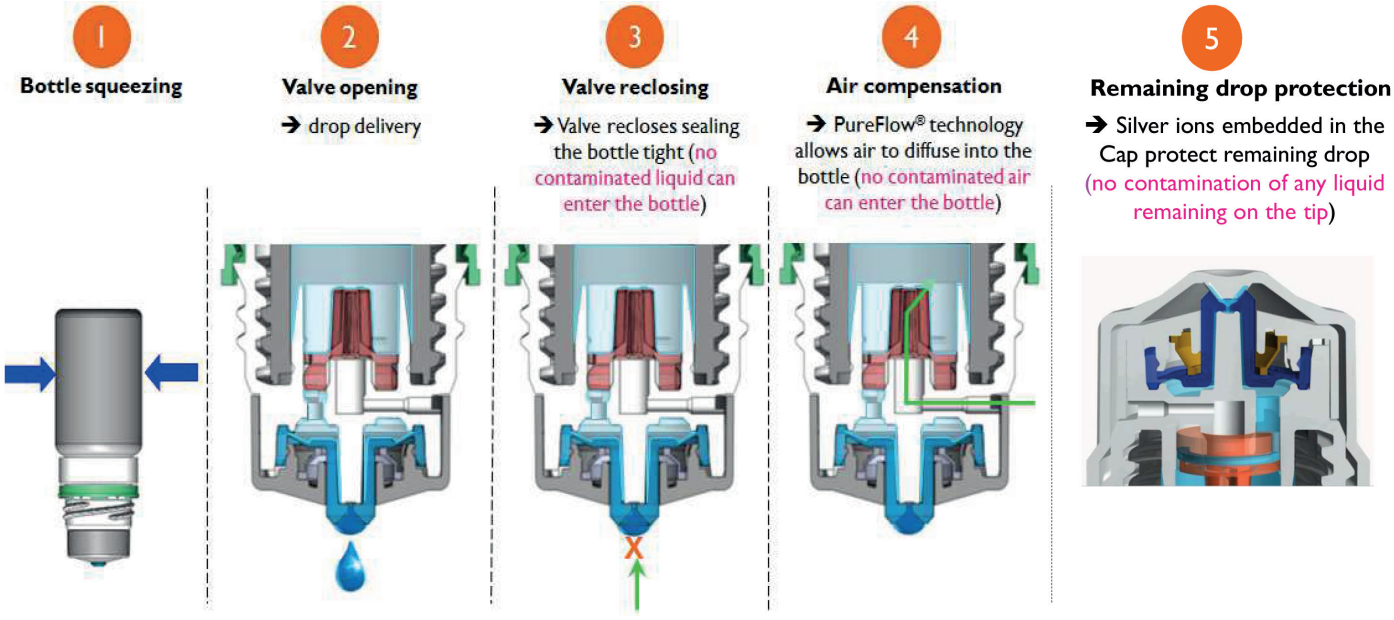

Figure 4: Novelia® functioning in five steps.

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the manufacturing process for the Novelia® platform.

Novelia is manufactured in a specific ISO7 clean room, with injection machines for plastic components and a fully automated assembly line. Half of the line is dedicated to inspecting every single product on all critical functions to ensure that Novelia® is perfectly safe for every patient.

Nemera industrial teams were involved right from the conception of the product and their input was incorporated into the design, so that Novelia® could be manufactured in high volumes while guaranteeing the required quality.

Regulatory requirements have been consolidated from the start of the development. Solid design history and regulatory files are available to help our customers register their formulation with our delivery system. We support them in their registration process to secure the product launch.

Q Could you talk about what unique benefits Novelia® brings to the patient?

A As we already discussed, we conceived Novelia® by putting ourselves in the patient's shoes. We designed the product with several patient-focused features, as the "blue tip", the low squeeze force and the PureFlow® technology.

There are some other important ways in which we considered the patient during the design of Novelia® in order to ensure that the system delivered the best possible patient experience. So, we knew we wanted a multi-dose system for preservative-free formulations. For this we could have chosen a pump system instead of a bottle. And we could have gone for a snap-on / snap-off cap rather than a screw cap. We decided on a bottle with a screw-cap because it is more convenient for patients to take their drops in this way. It is a system they are already used to. The patient unscrews the cap, turns the bottle upside down and squeezes the bottle to deliver the drop from the nozzle. We wanted to retain these simple and familiar steps.

Another key aspect was of course safety. We can't possibly have any contamination in the bottle. That's why we developed the one-way valve that prevents all backflow. No liquid can come back into the bottle. Another feature that keeps the drug free from contamination is the PureFlow® system. We conducted comprehensive microbiological challenge tests – to check the safety of the product. These have shown the system is safe even when exposed to severe contamination.

There were also safety advantages with the screw-cap. Whatever the conditions of use, the screw cap does not come off, whereas if you use a snap-on cap it can get loose after a while and it can come off in your pocket or bag.This is undesirable because of formulation leakage and contamination hazards.

As I mentioned, we conducted user tests with Novelia® several times during its development, building on patient feedback to improve the product. We also designed a study to assess patient preferences comparing multi-dose eyedroppers for preservative-free formulations. Novelia® stood out as the preferred device. This is rewarding because at Nemera our motto is always to put patients first and we can see that we have succeeded when patients put Novelia® first.

Q Thinking about Nemera more generally, how does ophthalmic drug delivery fit with the wider Nemera organisational structures and strategies?

A Ophthalmic is one of the four strategic franchises at Nemera. Multi-dose eyedroppers for preservative-free formulations is still a budding market, bound to boom in the next ten years. We are growing very aggressively in this area and we will help many more patients with their eye treatments in the future. Novelia® is manufactured near Lyon, France, at our La Verpillière facility, which is also where Nemera has its headquarters and Innovation Center.

Q Finally, please could you tell our readers a little about yourself? Describe your career and interests and experiences in and around ocular drug delivery, and tell us what is it about Nemera in particular that makes it attractive organisation to be a part of?

A I discovered the drug delivery business six years ago when I joined Nemera. For me it was a big change because I was coming from the chemical industry. It was very different – in the chemical industry it took several months to develop and manufacture a new product whereas in the drug delivery industry it takes several years! However, while it moves more slowly in that respect, it is so rewarding working to really improve patients' lives and put myself in the patient's shoes. Nemera is a wonderful company to work for. It's very dynamic and we have so many smart people. It's fun! I truly like working there.

ABOUT THE COMPANY

Nemera is a world leader in the design, development and manufacture of drug delivery devices for the pharmaceutical, biotechnology and generics industries. Nemera's services and products cover several key delivery routes:

- Ophthalmic
- Nasal, buccal, auricular
- Inhalation
- Parenteral
- Dermal and transdermal.

Nemera always puts patients first, providing the most comprehensive range of devices in the industry, including innovative off-the-shelf systems, customised design development, and contract manufacturing.

Nemera

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