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OPHTHALMIC DRUG DELIVERY

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

EDITORIAL CALENDAR

Feb 2020	Prefilled Syringes & Injection Devices
Apr	Pulmonary & Nasal Drug Delivery
May	Injectable Drug Delivery
Jun	Connecting Drug Delivery
Jul	Novel Oral Delivery Systems
Aug	Industrialising Drug Delivery
Sep	Wearable Injectors
Oct	Prefilled Syringes & Injection Devices
Nov	Pulmonary & Nasal Drug Delivery
Dec	Connecting Drug Delivery
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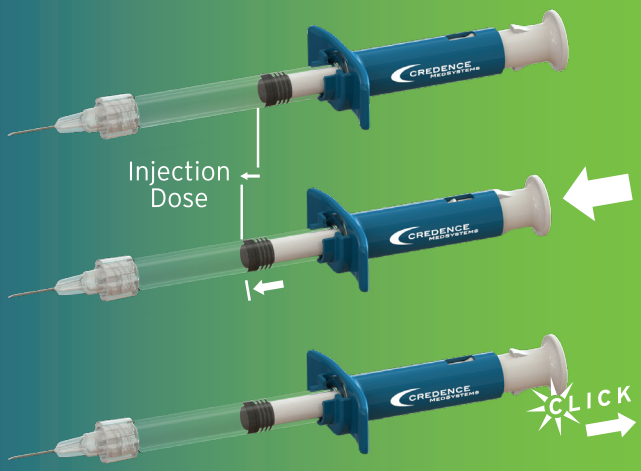

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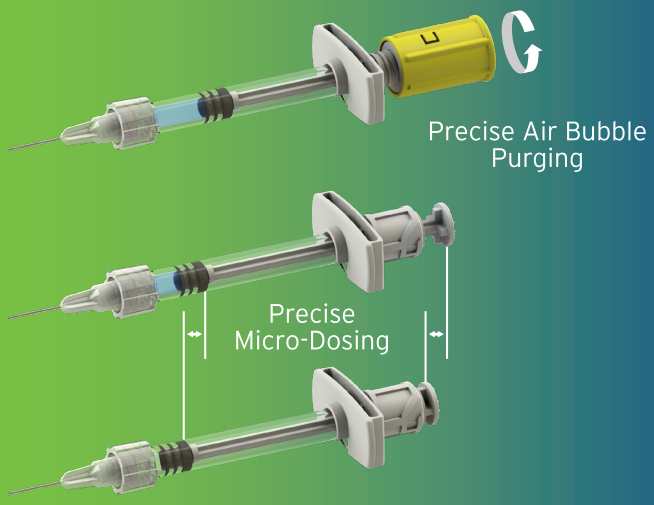

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ADVANCED DRUG DELIVERY FOR DRY EYE TREATMENT

In this article, Rouven Kraus, International Sales, Aero Pump, and Wilfried Woesthuis, Business Development Director, Consumer Health, Medspray, discuss their new open-eye spray for the treatment of dry eyes.

If you go to a drugstore and look for a medicine to treat your dry eyes, you will see that such moisturising products are usually packed in eye droppers. But the use of eye drops can be challenging, especially for elderly people. The patient has to tilt their head back, hold their eye open and squeeze the bottle so that the drop goes into the eye.

Eye sprays can be used as an alternative for patients who feel unable to use eye drops. The vast majority of eye sprays currently available on the market are applied to the closed eye. These rehydrating eyelid sprays are often based on a liposomal formulation, soy lecithin or sodium hyaluronate, offering hydrophilic properties.

Dry eye disease is divided into aqueous-deficient dry eye (20%) and evaporative dry eye (80%).[1] Liposomal eye sprays are specifically designed to address evaporative dry eye symptoms. Liposomes stabilise the lipid layer at the lacrimal film to improve the hydration of the ocular surface. The spray is applied onto the closed eyelid. The eye is kept closed for a few seconds, allowing the liposomes to reach the lid edge. Opening the eye spreads the artificial tear film across the entire eye surface.

> "The new eye spray can be applied from a close distance and from the front, directly onto the open eye, without causing a blink reflex."

But why not apply the formulation from a close distance onto the naked eye, by spraying an extremely fine and soft mist that avoids the blink reflex of the eye?

A CONVENIENT WAY TO TREAT DRY EYE

Aero Pump now offers such an alternative that is completely new to the market. Besides its preservative-free multi-dose eye dropper using 3K technology, Aero Pump has developed, together with its partner Medspray, innovative drug delivery technology for a topical ocular treatment.

The new eye spray can be applied from a close distance and from the front, directly onto the open eye, without causing a blink reflex. The unique ultra-soft fine mist delivers such small droplets the patient barely feels it (Figure 1).

The new open-eye spray is a preservative-free multi-dose device offering metered dose applications directly to the surface of the eye. The spray delivers an accurate 45 µL dose (dosage adaption possible).

Comfort and ease of use played a crucial role in the product development. The open eye spray completes Aero Pump's range of ophthalmic drug delivery devices, offering an alternative to eye droppers.

The innovation is based on a horizontal pump in combination with a micro- and nanotechnology-based spray

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Figure 1: The eye spray targeting the open eye without blink reflex.

nozzle that creates an ultra-soft, slow-moving fine mist by microdiffusion. The horizontal pump is designed to release the aqueous formulation first after a defined pressure. Then the liquid is accelerated and pushed through a tiny spray nozzle unit (SNU), developed by Medspray. The SNU (shown in Figure 2 positioned on the head of a match for scale) is composed of multiple micro-holes. In comparison, existing eye sprays only have an insert with just one output.

Based on the Rayleigh principle, whereby a liquid jet spontaneously breaks up into droplets, Medspray's patented SNU breaks up jets into mono-disperse droplet trains (Figure 3). As an example: a 5 µm hole creates a jet, breaking up into 10 µm droplet trains. The diameter of the droplets is twice the size of the orifice.

"The new eye spray is compatible with many of the well-known eye drop brands."

Medspray's SNU was developed at the nanolab of the University of Twente (Enschede, The Netherlands). The manufacturing process is based on established micro- and nanotechnology. The orifices of the spray nozzles are extremely tiny (1–30 µm). For reference, a human hair is about 70 µm thick. Engineering the size (1–30 µm), number of holes (1–200), vectors and geometric pattern means the spray characteristics can be tailored to different applications to meet specific industry partner requirements.

"It can be applied in a comfortable head position without the need to tilt your head back."

COMPATIBILITY WITH A WIDE RANGE OF OPHTHALMIC SOLUTIONS

Medspray conducted extensive formulation acceptance tests with several ophthalmic products from the market. The results of such studies show that the new eye spray is compatible with many well-known eye drop brands. The formulation has to be in an aqueous viscosity level. Even some formulations in the higher viscosity level can be applied through the SNU. The adjustable pore size of the SNU allows it to cover a wide range of ophthalmic solutions.

The formulation acceptance tests (FAT) were performed with several well-known ophthalmic brands for dry eye relief. Low-viscous as well as high-viscous products in the range of up to 125 mPas (e.g. hyaluronic acid) passed the FAT with Medspray's SNU. So it suggests the new eye spray is compatible with a wide range of ophthalmic solutions.

MAXIMUM PATIENT COMFORT

With the ultra-soft, slow-moving fine mist generated by the SNU – that even sensitive users will barely feel – the new eye spray can be easily administered onto the open eye. Furthermore, it has a great advantage over eye drops – it can be applied in a comfortable head position without the need to tilt the head back. This is especially beneficial for infants and the elderly.

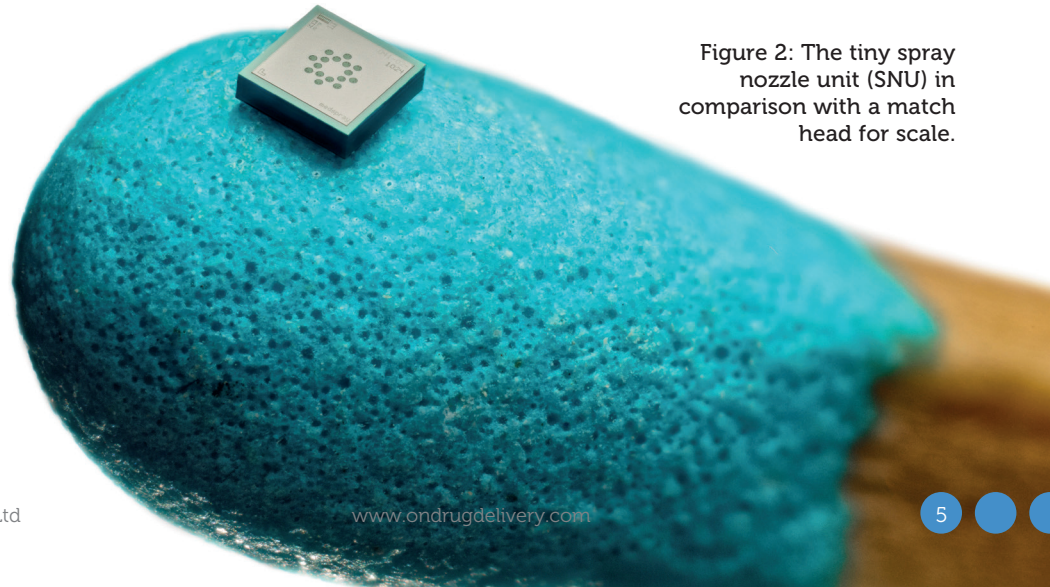

Figure 2: The tiny spray nozzle unit (SNU) in comparison with a match head for scale.

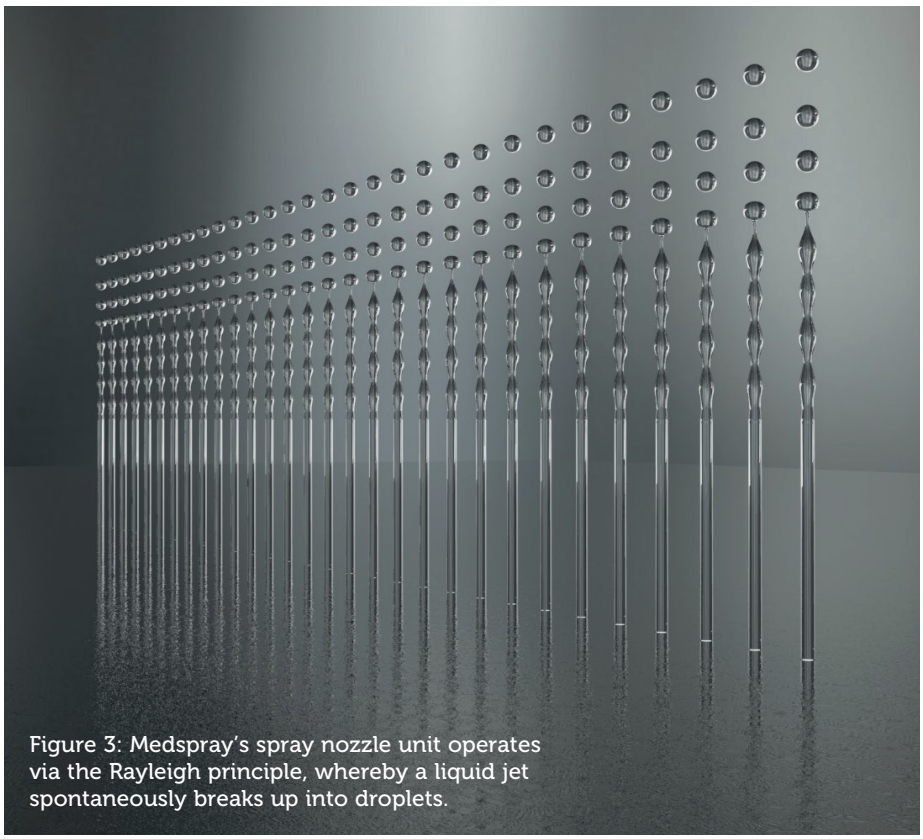

Figure 3: Medspray's spray nozzle unit operates via the Rayleigh principle, whereby a liquid jet spontaneously breaks up into droplets.

The droplets are so small that it avoids smudging of make-up, even from a close distance. The new eye spray can also be used with contact lenses.

The device is protected from microbiological contamination, so there is no need to add preservatives to the formulation. The pump technology offers propellant-free spray solutions so it is also eco-friendly.

Aero Pump is setting up serial production of the eye spray this year at its facility in Hochheim (Germany).

ABOUT THE COMPANIES

Aero Pump is a leading manufacturer of high-precision application systems for the pharmaceutical and healthcare industry, focused on innovation, multi-functionality and contemporary design. Its spray pumps and dropper systems are widely established in the market and are primarily used in the ophthalmic, nasal, pulmonary and topical fields, suitable for preserved and preservative-free over-the-counter and prescription drugs.

Medspray develops innovative spray nozzles for user-friendly consumer health (nasal, ophthalmic, topical), pharma and personal care products. By making propellants redundant and increasing user friendliness, Medspray offers added value both to its clients and their end users. The Medspray nozzles can be used for various purposes, especially where a slow-moving, soft spray is required. Thanks to the high-tech nozzle chips, sprays can be tailored to suit any application.

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ABOUT THE AUTHORS

Rouven Kraus has more than seven years of experience in the ophthalmic drug market. He joined Aero Pump in 2012 in the field of business development for drug delivery devices. His responsibilities include sales co-ordination for the European, US, Far East and Middle East markets. He is also responsible for the company's strategic approach to new ophthalmic developments and delivery technologies.

Wilfried Woesthuis, Business Development Director, Consumer Health, Medspray, graduated with a degree in marketing and business administration from the Saxion University Enschede, The Netherlands. Before joining Medspray in 2019, he had several international marketing and sales management roles at leading global medical device manufacturers. At Medspray he drives development projects for new over-the-counter ophthalmic, nasal and topical spray products, which include the company's patented spray nozzle units.

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DELIVERING ON THE GROWING NEED FOR TOPICAL PRESERVATIVE-FREE OPHTHALMIC TREATMENTS

In this article, Matthias Birkhoff, Vice-President Business Development, Aptar Pharma, provides an overview of the existing technologies available in ophthalmic drug delivery and the progress made within topically applied medications – and introduces a new market standard for testing microbial integrity in preservative-free formulations.

Ophthalmic therapeutics, along with more general vision care, are vital components of the global healthcare landscape due to their very demonstrable impact on the quality of life for patients with ocular disorders.

As such, ophthalmic drugs represent a significant part of the global pharmaceutical market, with sales of more than US$24 billion (£18.5 billion) annually in 2018. This figure continues to grow across the world as there is an increasing prevalence of eye disorders, particularly among the elderly population. Retinal disorders such as age-related macular degeneration (AMD), diabetic retinopathy (DR) and diseases such as presbyopia, dry eye syndrome, glaucoma, conjunctivitis, red eye and uveitis are driving growth in ophthalmic treatment needs. In addition, the general increase in consumer demands and spending power in emerging markets such as Brazil, Russia, China and India also contributes to a sales growth.

WE NEED TO KEEP AN EYE ON THE CHALLENGES

The success of any drug discovery and development programme requires true collaboration between formulation scientists and device manufacturers. This collegiate approach is no different in ophthalmic drug delivery. Indeed, some may conceive it as even more critical to success than in any other delivery route, particularly when trying to address unmet needs in the treatment of eye disease.

There are, however, some challenges associated with ophthalmic drug delivery. Undoubtedly, the primary way to administer eye medications remains by means of topical drops. Even today, novel intraocular pressure (IOP) reducing medications are administered as topical eye drops. But, at the same time, development of sustained release delivery technologies for treatment of ophthalmic diseases has made substantial progress and is considered to increase patient compliance and achieve a higher therapeutic benefit.

Looking at retinal disorders, almost all available treatments require invasiveprocedures since none of the currently available therapeutic alternatives offer options for topical administration. However, it seems fair to assume that patients prefer to take drops rather than receive injections into their eyes. This all makes the "traditional" way of administering ophthalmic medications worth considering, even in the future. This method does, of course, rely heavily on the patient's willingness and ability to administer the product and the perceived side effects associated with such administration.

Also the increasing cost pressure from payers needs to be taken into consideration. Healthcare systems around the world are very different, with some patients bearing all the costs and others none or just a fraction. In particular, the latter ones will continuously look for costing improvements while the ever-ageing population continues to grow, as does demand for age-related ophthalmic treatments.

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With these aspects of cost effectiveness and security-of-supply in mind, it is fair to conclude that it will be very difficult to rely entirely on invasive methods and treat patients properly without topical ophthalmic medications. Given these considerations, it makes sense for innovative pharma companies to develop topical administrations in a way that patients and consumers can embrace.

WHILE NECESSARY FOR SAFETY AND STABILITY, PRESERVATIVES PRESENT PROBLEMS

The use of preservatives in eye-care formulations – both prescription and over-the-counter products – has come into sharp focus in the past few years. Preserved topical medications have been the mainstay of treatments for patients prescribed with varying lengths of regimen. In most of the ophthalmic medications, preservatives are therefore required to prevent the growth of microbial contaminants, mitigate against biodegradation and keep the drug product stable and safe over time.

However, historically used preservatives, such as benzalkonium chloride, are known to have tolerability issues in patients. Indeed, some preservatives themselves present a risk, with clinical data[1] suggesting that continuous exposure to certain preservatives can result in various side effects such as ocular surface changes, ocular discomfort, tear film instability, conjunctival inflammation, subconjunctival fibrosis, epithelial apoptosis, corneal surface impairment, subclinical inflammation and even the potential risk of failure in further surgical interventions. Such adverse reactions can have an impact on patient adherence – especially in chronic diseases, like glaucoma, which require lifelong therapy with topical treatments for the eyes.

DEVELOPING CHALLENGING TEST METHODS

A formulation containing no preservatives has its own challenges too, of course, and requires specific measures to ensure sterility, microbiological integrity and, therefore, patient safety. The key question in a preservative-free, multi-dose (PFMD) device must be how the pharma manufacturer can deliver enough evidence to show that, even under highly challenging conditions, microbiological integrity is maintained during shelf life and in use.

In the absence of guidelines regarding multi-dose containers for unpreserved ophthalmic preparations, test methods proving a microbial barrier function need to be carefully selected. However, there has been much progress in test methods since their introduction in the 1990s for the first PFMD systems, and Aptar Pharma strongly believes its recently published method TSIT 2.0 (tip-seal integrity test) is as close to a universal standard as the industry has right now.

Initial tests were developed to show safety of systems that contained silver ions in the plastic material of the dispensing system. The so-called Wiedemann[2] test was developed according to the particularities of such systems, which release the abovementioned silver ions into the formulation. The acceptance criteria are a low microbial burden of the delivered dose and no contamination of the bottle.

In 2004, a tip-seal integrity test was developed using the same challenge germs but adding more challenging handling conditions.[3] This test has been reviewed by agencies such as the US FDA and has enabled, among others, the launch of Allergan's Restasis MultiDose in 2016 – the first FDA-approved prescription medication using a PFMD eye dropper, Aptar Pharma's Ophthalmic Squeeze Dispenser (OSD). In 2019, Santen's prescription drug Taflotan/Saflutan for the reduction of elevated IOP in open angle glaucoma and ocular hypertension was approved in 26 countries in Europe, again using the Aptar Pharma OSD (Figure 1).

Most recently, the TSIT method was further developed to align it more closely with the preservative-free tests described in the US Pharmacopeia (USP) <51> and European Pharmacopoeia (EP) 5.1.3.[4] Aptar Pharma developed this method in order to provide a reasonable and standardised challenge procedure for PFMD-systems (Figure 2).

Today, the TSIT 2.0 procedure provides a significant challenge for PFMD devices as it uses a relevant challenge scenario. Combined with an analysis of the microbial properties of the formulation (growth promoting, growth inhibiting or even

Figure 1: Taflotan (tafluprost) as marketed by Santen (Image courtesy Santen), and Restasis (cyclosporine) as marketed by Allergan (Image courtesy Allergan), both of which use Aptar Pharma's Ophthalmic Squeeze Dispenser (OSD) platform.

bacteriostatic), as well as including two more germs, this method is well suited for the risk evaluation of new PFMD delivery systems. It indicates, using transparent, science-led data, that patients, physicians and the regulatory authorities can be certain about the safety of tested preservative-free ophthalmic medications (Table 1).

TSIT 2.0 HELPS FACILITATE MARKET ACCESS

Aptar Pharma's US FDA- and German BfArM-reviewed Ophthalmic Squeeze Dispenser is a multi-dose technology designed specifically for preservative-free ophthalmic formulations. Suitable for a wide range of viscosities, it offers pharma

"The Ophthalmic Squeeze Dispenser's unique safety profile contributes to the fact that it remains the only FDA-reviewed multi-dose system for unpreserved ophthalmic formulations."

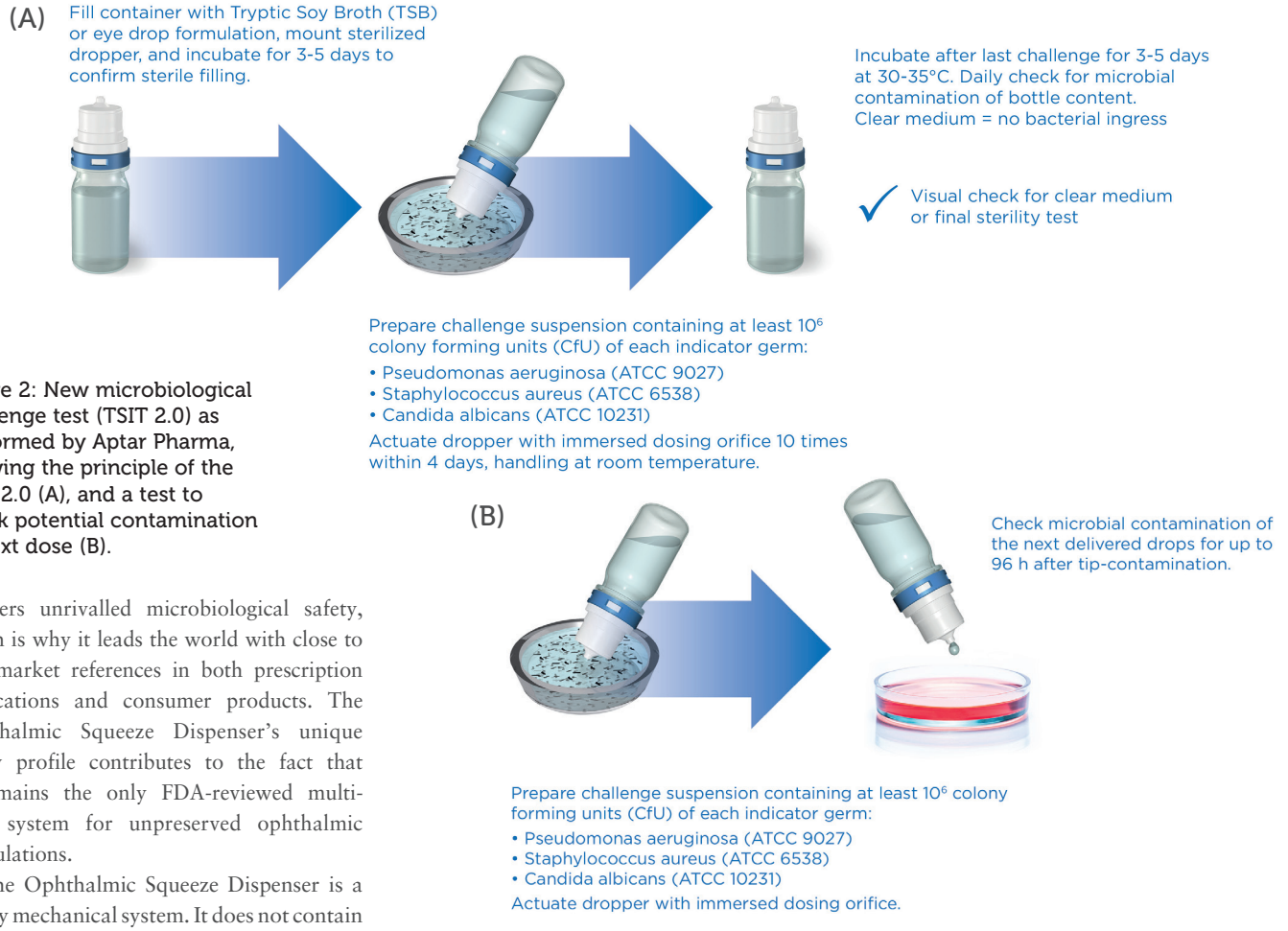

Figure 2: New microbiological challenge test (TSIT 2.0) as performed by Aptar Pharma, showing the principle of the TSIT 2.0 (A), and a test to check potential contamination of next dose (B).

partners unrivalled microbiological safety, which is why it leads the world with close to 250 market references in both prescription medications and consumer products. The Ophthalmic Squeeze Dispenser's unique safety profile contributes to the fact that it remains the only FDA-reviewed multi-dose system for unpreserved ophthalmic formulations.

The Ophthalmic Squeeze Dispenser is a purely mechanical system. It does not contain any questionable additives that increase the complexity of approval processes or lead to constraints within the patient population. The tip of the orifice is protected with a sealing mechanism that – with proven reliability - avoids any microbiological ingress, while the air which is required to equilibrate the system passes a 0.2 µm filter membrane that is subject to 100% online inspection during manufacturing (Figures 3 and 4).

MULTI-DOSE, PRESERVATIVE-FREE DEVICES ADDRESSING UNMET NEEDS

Retinal disorders, such as diabetic macular oedema, are leading causes of blindness. In fact, the WHO estimates that 11% of the 347 million people suffering from diabetes also suffer from diabetic retinopathy. The gold standard treatment for this and other retinal diseases is currently anti-VEGF drugs which require frequent intravitreal injections. Obviously, this is an expensive strategy, and recent data shows that compliance with such therapies is not ideal.[5]

Formulation scientists around the world are working on ideas to allow drugs to penetrate corneal and scleral structures without invasive procedures. The ultimate goal is to have anti-VEGF drugs as topically administered drops. Such formulations would clearly benefit from being preservative-free, as they would be for long-term treatments.

A SAFE, STABLE & SUSTAINABLE OPTION

What about single-use vials – also known as blow, fill and seal (BFS) technology? Before PFMDs were developed, BFS products were the only option for preservative-free ophthalmic formulations for topical treatments. Ophthalmic preparations can be filled and administered without the use of preservatives, and with a single use the risk of contamination is extremely low, provided neither patients nor consumers try to "stretch" the use of their vials, i.e. keep them for multiple use. The internet is full of instructions and "competitions" about how long one can use a single dose vial. Such strategies certainly do not contribute to the safety of ophthalmic medications.

Another challenge with single-dose applications is the pure amount of packaging they generate. BFS packs require a great deal of plastic and paper, as well as complex aluminium-based laminates used for pouching the single dose units – creating an additional environmental burden, both in terms of manufacturing and recycling. Proprietary research conducted by Aptar Pharma shows its Ophthalmic Squeeze Dispenser 10 mL multi-dose device generates a significantly smaller CO_2 footprint than the equivalent in single-dose systems.

BETTER CONNECTED DEVICES ENABLE BETTER PATIENT OUTCOMES

The final element in the compliance trinity is the increased use of connectivity. With soaring clinical trial costs and complexity, the biopharma industry is constantly seeking new approaches to improve efficiency and productivity. Aptar Pharma has teamed up with Kali Care (Mountain View, CA, US) to create a digital monitoring system for ophthalmic medications that will help reduce the costs and complexity of ophthalmic clinical trials.

This revolutionary sensor technology allows clinicians to replace adherence assumptions in clinical trials with collected real-time patient data that can be automatically integrated. This can result in shorter and more efficient clinical trials. Such an automatically generated adherence score provides critical

	Wiedemann Test	Established Aptar TSIT	TSIT 2.0
Rationale for test	Test was developed and optimised for Comod® and 3K® System (1993-94)	Aptar TSIT adapted ~2004 to APF nasal spray pump	Request from authorities (e.g. BfArM) for broader challenge based on antimicrobial effectiveness testing EP 5.1.3 USP <51>, <771>
Test medium	Physiological saline	Growth medium	Growth medium, tryptic soy broth (TSB)
Indicator germs	Pseudomonas aeruginosa ATCC 9027 $>10^6$ CfU/mL	Pseudomonas aeruginosa ATCC 9027 $>10^7$ CfU/mL	Pseudomonas aeruginosa, ATCC 9027 Staphylococcus aureus ATCC 6538 Candida albicans ATCC 10231 At least 10^6 CfU/mL for each germ
Challenge procedure	Tip submersed in challenge suspension, then removed and actuated, 8 times within 4 days	Tip submersed in challenge suspension and actuated, 10 times within 5 days	Tip submersed in challenge suspension and actuated, 10 times within 4 days
Incubation temperature	During challenge period ambient temperature, afterwards at 32°C	Whole test period at 32°C	During challenge period ambient temperature (20-25°C), afterwards at 32°C
Parameters analysed	Analysis of spray and container content	Analysis of spray and container content	Only analysis of container content (other parameters may be included on request)

Table 1: Test procedures for PFMD systems.

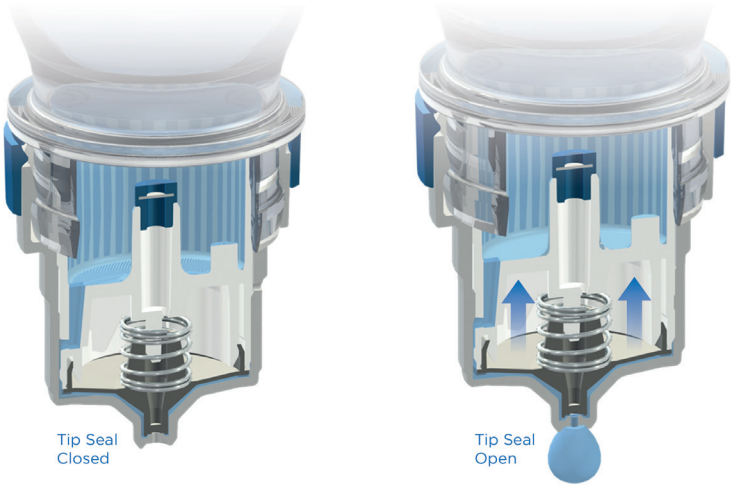

Figure 3: Aptar Pharma's proprietary, purely mechanic tip-seal mechanism used in the Ophthalmic Squeeze Dispenser.

Figure 4: Close to 250 prescription medications and consumer products have been successfully launched with Aptar Pharma's Ophthalmic Squeeze Dispenser.

information for explaining the incongruity between recommended treatment and actual treatment outcomes (Figure 5).

Various clinical trials have reported average adherence rates of only 43-78% among patients receiving treatment for chronic conditions.[6] In clinical practice, the ability to see the medication-adherence score of patients with glaucoma is a powerful tool for ophthalmologists. In a very short time, we believe we will see devices optimised for orientation and pressure.

Aptar Pharma has been setting the standard for the drug delivery industry for decades. This collaboration with Kali-Care once more underlines the company's continuous efforts in breaking new ground in innovative healthcare technologies.

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is a go-to drug delivery expert, providing innovative drug delivery systems, components and active packaging solutions across a wide range of delivery routes, including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma Services provides early-stage to commercialisation support to accelerate and derisk the development journey. With a strong focus on innovation, Aptar Pharma is leading the way in developing connected devices to deliver digital medicines. With a global manufacturing footprint of 14 GMP sites, Aptar Pharma provides security of supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc (NYSE: ATR).

(A)

(B)

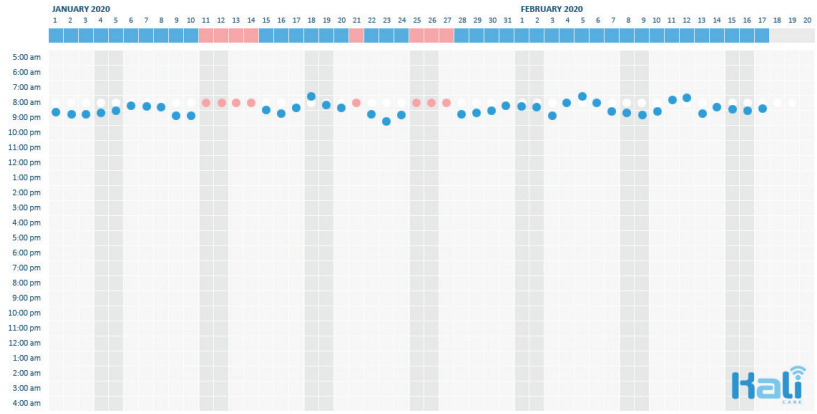

Figure 5: Typical motion sequence of administering eye drops, recorded with Kali Care's sensor technology (A). Collection of objective real-time data results in reliable adherence charts (B).

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ABOUT THE AUTHOR

Matthias Birkhoff is Vice-President Business Development at Aptar Pharma. In this role he is responsible for Aptar Pharma's eye-care programme and co-ordinates research and development activities, microbiological assessment and commercial strategies. Mr Birkhoff started his career in sales at a major multinational pharma company before joining Aptar Pharma 19 years ago. Prior to his involvement in business development and marketing, he oversaw sales in the Asia Pacific region. He studied medicine at the University of Dusseldorf, Germany, and holds a nursing degree.

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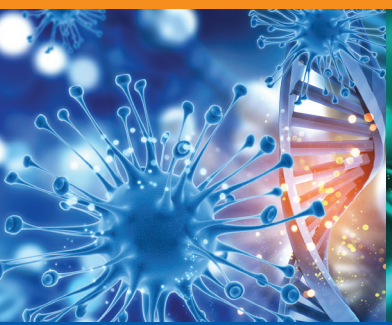


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DEVELOPING AN EFFICIENT OPHTHALMIC DEVICE COMBINATION PRODUCT

In this article, Zoë Davidson, Global Category Manager – Ophthalmic, at Nemera, looks at how understanding the patient journey can help develop an efficient ophthalmic device combination product.

A significant patient population suffers from conditions requiring long-term daily use of eye drops. Dry eye syndrome is associated with ageing, contact lens use and environmental factors. 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 six times a day, often for the rest of the patient's life. Other chronic conditions, such as glaucoma and hayfever, also require the long-term use of self-administered eye drops.

The majority of eye drops today contain preservatives to maintain the formulation's sterility. The most commonly used preservative is benzalkonium chloride, which is known to damage the cornea over long-term use. Preservatives can also cause allergies or ocular irritation, and some can even cause a toxic response.[2] Any such reactions are particular issues for patients who rely on the long-term use of eye drops for chronic conditions.

THE POWER OF PUREFLOW TECHNOLOGY

To prevent the entry of bacteria into the bottle and/or to filter air, more than half of bottles designed for multi-dose preservative-free eye drops on the market rely on a filtering system – with 0.22 µm sterile mesh filters being the industry standard. But significant research has been carried out that challenges their effectiveness.[3] Due to their porous structure, bacterial filters do not provide a continuous barrier to contamination.

Nemera's 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. The non-return 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 Novelia dispenser takes place via a separate venting system with a silicone membrane called PureFlow Technology (Figure 1). The silicone membrane is a solid, non-porous (unlike bacterial filters) material. It is homogenous and does not contain any holes – therefore its characteristics can be precisely engineered.

As well as serving as a venting system for air diffusion into the bottle, Novelia's PureFlow has a second function: flow control. Nemera has adapted the flow-control technology within Novelia that avoids multiple drop delivery into the eye and ensures that only one calibrated drop is dispensed at a time. Nemera offers three different PureFlow versions, each tailored to formulations of differing viscosities, from highly liquid to highly viscous.

NOT JUST A PRODUCT BUT A PLATFORM

Novelia is not just one product but a platform, designed and developed with patients in mind. The demands of the ophthalmic market are increasingly varied in terms of new formulations and compositions. That's why adaptability is a key criteria for Nemera.

Available to Novelia are five different valve sizes, each one delivering a different calibrated drop size. This allows Nemera's team to customise the drop size depending on specific product requirements – a factor

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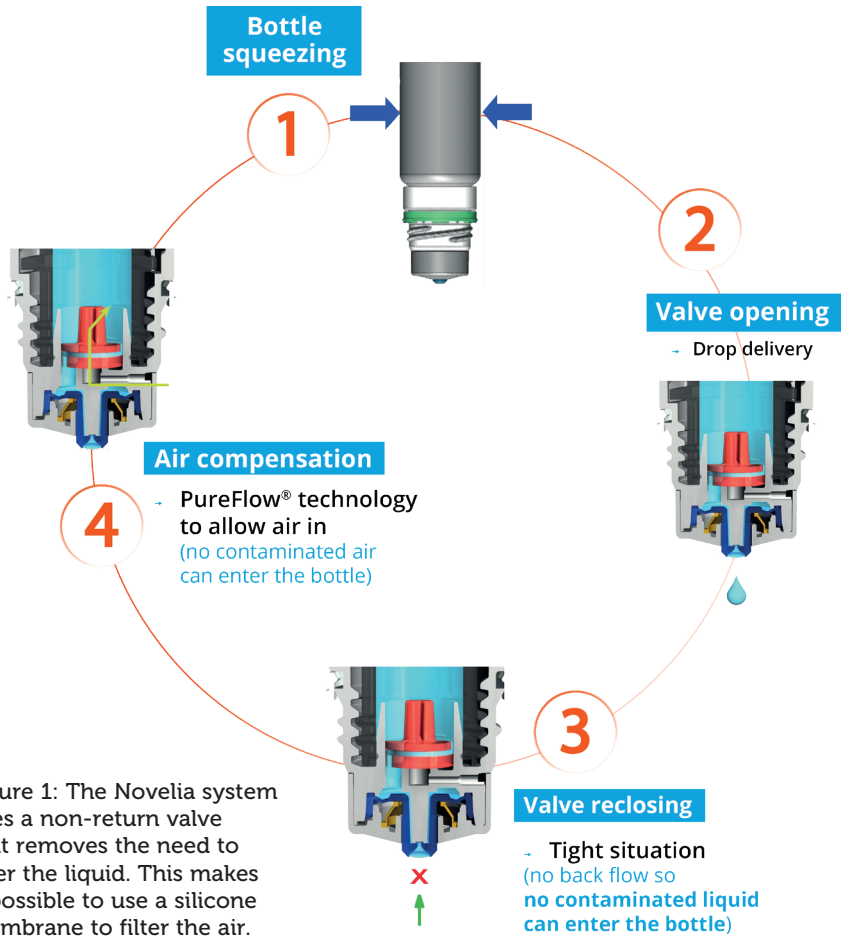

Figure 1: The Novelia system uses a non-return valve that removes the need to filter the liquid. This makes it possible to use a silicone membrane to filter the air.

which is particularly important for generics companies where the generic product must replicate the same drop size, as well as the composition, of the originator product.

A range of bottles is available in terms of size, material and sterilisation type: 5 mL, 7.5 mL, 11 mL and 15 mL (Figure 2). All sizes are available in low-density polyethylene. The Nemera is also developing polypropylene and cyclic olefin copolymer bottles for specific formulation compatibility. Novelia has been validated using both gamma and ethylene oxide sterilisation. Offering two options for sterilisation allows Nemera to meet customers' compatibility needs better.

In addition to Novelia's standard white cap colour, Nemera is able to develop additional colours for specific demands. Additional cap options include a vented cap, designed for sticky formulations, and a child-resistant cap.

NOVELIA PREFERRED BY 76% OF PATIENTS

"We put patients first" is not just a motto used by Nemera but an attitude firmly ingrained in the company's culture. The earlier Nemera can include patients in the development phase to assess their behaviour versus new design, the better. Patients' needs and constraints are generally identified when defining the product design brief and are included in Nemera's quality process and documents such as product specification, design and user failure mode effects analysis.

In 2015, Nemera had user tests carried out by an independent company.[4] The panel of patients interviewed fell into two main criteria: demographics (age, gender) and type of eye condition (glaucoma, dry eye, etc.). These patients were interviewed in their own homes in both the US and the UK. These tests concluded that 76% of patients interviewed (68 out of 90 users) preferred Novelia over other similar devices on the market (Figure 3). Contributing factors to Novelia preference included the intuitiveness of the screw-on cap and the associated reassurance, and the squeeze force required towards the end of the product's life. Novelia required only 6% more pressure to squeeze the bottle from the beginning to the end of the treatment, compared with 35% for the other device.

Originally intended to be transparent, Novelia's patented blue tip was the result of a previous user study, where patients signalled that a coloured tip would help them target their eye. This feature was another aspect favoured by patients during the 2015 study.

> "Effective drug delivery and patient adherence to treatments are increasingly important considerations in ophthalmology."

SUPPORTING CUSTOMERS BY OFFERING A RANGE OF SERVICES

No single formulation is the same as another. Each has its own set of characteristics, such as viscosity or look (emulsion versus gel, for example), which impact its behaviour and delivery to the patient.

Figure 2: Novelia has a full range of bottles available in terms of size, material and sterilisation type.

Figure 3: 76% patients preferred Novelia compared with other preservative-free multi-dose eye droppers on the market.

Nemera offers a range of laboratory services, including testing of customers' bulk formulation. This testing comprises usage simulation over a two-week period, drop size analysis (variable depending on valve diameter), flow control and squeeze force testing (beginning and near end of life). The culmination of these tests results allows Nemera to determine the best Novelia configuration for a particular customer formulation. Nemera can recommend the most suitable PureFlow control, bottle type and valve size to achieve the desired drop calibration.

Nemera can also assist customers in finding the right ready-to-go dossier available for private labelling certain molecules with the Novelia device. Nemera has a list of partners, formulation licensors and fillers, all working in collaboration to bring customers a finished drug device combination with Novelia.

Finally, with more than 160 references on the market for prescription and over-the-counter products, Nemera's regulatory team is on hand to support customers with their submission filing and provide guidance on supportive documents for registration.

CONNECTED DEVICES HAVE A ROLE IN HELPING PATIENTS WITH ADHERENCE

In the case of chronic eye conditions such as glaucoma and dry eye – both of which require the patient to administer eye drops consistently over a long period of time – adherence is found to be low, particularly for glaucoma, a leading cause of irreversible blindness worldwide.[5-8] Nearly nine out of ten glaucoma patients are unable to instill eye drops correctly and therefore an easy-to-use system that is appreciated by patients could contribute to improving their compliance with a treatment.[9] With an ageing population and an increasing number of patients suffering from chronic eye conditions, effective drug delivery and patient adherence to treatments are increasingly important considerations in ophthalmology.

Nemera's answer to challenge the issue of poor adherence and improve the patient's experience is the development of e-Novelia – an add-on device to Nemera's existing preservative-free multi-dose eye dropper (Figure 4).

Using smart add-on technology, the patient benefits from digitalised and interactive instructions via their smartphone. Key features include providing patients with reminders on when to take their next dose and when to replace their medication, for example. The add-on can also track the number of drops delivered and when exactly they have been delivered (date and time), comparing the actual intake with the posology – thus calculating the patient's compliance. This new technology will not only be useful for patients but for the entire industry. Healthcare professionals will benefit from dose-tracking analysis, researchers will be able to perform more efficient clinical studies and pharmaceutical companies will be able to launch better-performing drugs.

UNDERSTANDING THE PATIENT JOURNEY

In August 2019, Nemera acquired Insight Product Development (Chicago, IL, US) – now Insight Innovation Centre – to complement its existing innovation centre at its headquarters in La Verpillière, France.

The acquisition combines the strengths of Insight Product Development in front-end innovation, design research, human factors and design engineering with Nemera's strong late-stage development, as well as clinical and commercial manufacturing capabilities. These newly enhanced capabilities now enable Nemera to offer end-to-end development services to all its customers globally and to collaborate with them earlier, supporting their complex drug delivery and medical device projects.

By conducting interviews in a natural home setting, familiar to the patient, Nemera is able to obtain a more accurate insight into how drug delivery devices are actually used. There is significant value to be derived from this method of understanding, characterising and prioritising user needs, which is best initially achieved through applied ethnography. This method relies on a combination of interviews and in-context observations of practices, processes and experiences within the patient's home, clinical environment or any natural setting. This approach can yield a deep, longitudinal understanding of the patient journey – from diagnosis, to treatment selection, to onboarding and ongoing use.

Figure 4: Nemera's e-Novelia ophthalmic add-on won the "Excellence in Pharma: Drug Delivery Devices" Award at CPhI Worldwide 2018.

A map of the patient journey provides a very powerful tool to drive inputs and decisions, especially when used in the earliest stages of a development programme. Thoroughly understanding the patient journey can then be leveraged as a critical early-stage road map to help inform selection of the appropriate device. This understanding can also help Nemera uncover patient engagement opportunities that can be supported with connectivity and mobile applications to support value-based care.

Nemera firmly believes that developing a holistic and comprehensive patient experience and human factors management strategy can create significant competitive advantages and ultimately result in safe, effective and differentiated combination products that respond to patient needs.

ABOUT THE COMPANY

Nemera is one of the world's leading designers, developers and manufacturers of drug delivery devices for the pharmaceutical, biotechnology and generics industries. It offers a comprehensive portfolio of products and services across ophthalmology, nasal, inhalation, dermal, transdermal and parenteral delivery. Its newly branded Insight Innovation Centre, with offices in North America and Europe, provides consultative services to support customers' overall device strategy. Providing user research, human factors, user experience design and design for manufacturing, the Insight Innovation Centre can help navigate device strategies for both novel and platform solutions.

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ABOUT THE AUTHOR

Zoë Davidson is the Global Category Manager for Nemera's ophthalmic franchise, including the preservative-free, multi-dose eye dropper Novelia. She joined Nemera in January 2017 as part of the business development team, responsible for ophthalmic products, before transitioning into the category manager role during the summer of 2019. Graduating in 2013 from Strathclyde Business School in Glasgow, Scotland, Ms Davidson studied International Business and Modern Languages. Prior to her move to Lyon, France, and joining Nemera, she held the position of International Marketing Executive for an award-winning independent company in the UK tourism industry.

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OPHTHALMIC • PARENTERAL • INHALATION • EAR NOSE THROAT • DERMAL

DR SRI MUDUMBA, SANTEN & DR GAUTAM SHETTY, CONGRUENCE

At the 2019 Parenteral Drug Association (PDA) Europe's Universe of Prefilled Syringes & Injection Devices meeting in Gothenburg, Sweden, Congruence Medical Solutions and Santen Pharmaceutical were presented with the Drug Delivery Innovation Award for their partnership to develop the Microliter Dosing Syringe (MDS) device platform. Award criteria included – being an innovation, solving an unmet need in the market, global market relevance and combining different technical expertise in developing a technical solution. Sri Mudumba, PhD, of Santen, and Gautam Shetty, PhD, of Congruence, received the award on behalf of their respective organisations.

Dr Mudumba is Vice-President of Therapeutic Modality Innovation at Santen – a global company focused solely on ophthalmology and committed to serving serious unmet needs by developing innovative solutions that protect and restore vision. He has been working in ophthalmology research and development for 15 years.

Dr Shetty is the founder of Congruence Medical Solutions. Prior to Congruence, he was General Manager of a novel drug delivery systems business unit at Unilife. He pioneered development of ophthalmic drug delivery devices and targeted organ delivery systems. In this interview, Drs Mudumba and Shetty share insights from their experience of working together in developing the MDS for ophthalmic injections.

Q Why did you identify the need for your ophthalmic drug product in a prefilled format?

SM Our product profile required an injection as low as 20 µL. I had investigated various options for prefilled syringe manufacturers and fill-finish contract manufacturing organisations (CMOs) and couldn't find anything that could deliver precisely 20 µL in prefillable format. We approached Congruence with this challenge and they came up with a solution. A prefilled syringe offers a lower fill volume (reduced drug product waste and increased batch yield ultimately offering lower cost of goods sold) than a vial. In addition to the product yield, from a customer-centric approach, a prefilled syringe is preferred as it involves less manipulation before injecting.

Figure 1: Gautam Shetty (right) and Sri Mudumba (centre) receiving the 2019 Drug Delivery Innovation Award from Thomas Schoenknecht (left), Chairman of the PDA Conference and member of the Awards Committee (Photo courtesy PDA).

GS It has been fascinating to observe the ophthalmic injection space since Lucentis (ranibizumab) was launched in June 2006 by Genentech (now part of Roche) – an incredible pharma innovation that transformed what was a suboptimal surgical intervention to treat blinding eye disorders into a successful pharma intervention. Since then, a growing number of pharma companies have innovated and continue to develop novel treatments that need injections in the eye – Santen being one of them.

The value proposition for prefilled syringes as applied in subcutaneous and intramuscular injection – streamlining

"Delivering a microlitre dose accurately and precisely using a syringe that typically delivers millilitre volumes becomes a key requirement."

injection procedure, reducing costs, driving customer preference, product differentiation – holds true in ophthalmology as well.

Q What are key requirements for an ophthalmic injection system? Are there unmet needs outside of ophthalmology?

SM It is critical that sterility is maintained throughout the eye injection procedure (reducing the number of steps in preparation of injection) to prevent any potential for infectious endophthalmitis. It is also important to minimise the burden on the physician for accurate dosing. Another factor that is becoming increasingly important is to minimise injection of non-drug impurities such as silicone oil into the eye.

GS There are a number of regulatory and compendial requirements unique to an ophthalmic drug delivery system. The commercialisation path of least resistance for a prefilled option requires incorporating standard container closure components into an ophthalmic injection system. Ophthalmic drugs are delivered in microlitre volumes, typically 50 µL or lower. Delivering a microlitre dose accurately and precisely using a syringe that typically delivers millilitre volumes becomes a key requirement. Also, considering that several drugs are still in clinical development, a microlitre injection system should be able to draw from a drug vial and then deliver an accurate, precise microlitre dose. In addition to the applications in ophthalmology, there are several emerging applications in oncology, neurology, dermatology and localised delivery that require delivery of microlitre-size volumes.

Figure 2: The Microliter Dosing Syringe (MDS) incorporates standard prefillable syringes, shown here with various 1 mL long prefillable syringes.

"Several syringe suppliers, who may have been left out of the microlitre dosing space, looked at the MDS as an enabling technology."

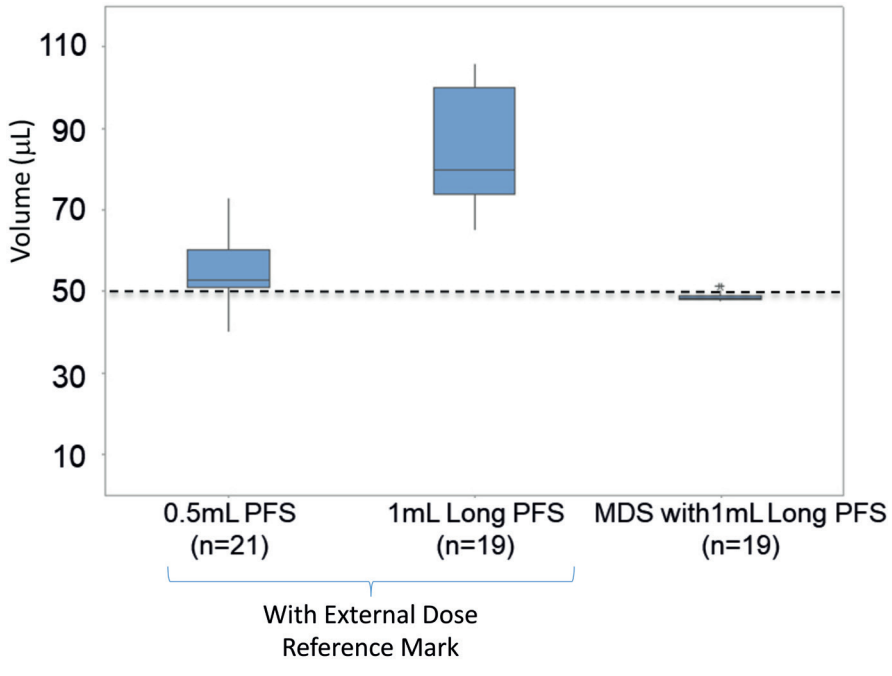

Figure 3: Ophthalmologists attempted to deliver a 50 µL dose using the MDS and conventional prefilled syringes.

Q Why and how did you decide to manage development of the MDS through an external partnership?

SM Santen's core expertise is not in injectable drug delivery devices and associated primary packaging. We constantly evaluate external partnerships that offer new technologies that will help our products in tiers. Microlitre dosing serves as an enabling technology when the existing commercially available syringes do not meet our criteria for low-volume accurate dosing. When trying to bring a best-in-class therapeutic onto the market, the delivery plays a big role. The MDS format (Figure 2) can be a key differentiator with a competitive advantage. In addition, as it takes a long time to ultimately commercialise a drug product, a device as a lifecycle-management tool becomes very critical for us. MDS can help us manage the lifecycle of the drug product as well. Finally, our core expertise lies in drug product development and not device development, so we decided to look for external partners who can help us build a prefilled syringe-based platform.

> "When trying to bring a best-in-class therapeutic onto the market, the delivery plays a big role."

GS There has always been a decision to make when an off-the-shelf delivery system is unavailable. Make or buy? Reasons for either option have been fairly well understood and broadly discussed in the industry. In this case, our background and specialised competence to develop a novel technology with the performance necessary for accurate, precise delivery within the constraints of standard pharma fill-finish infrastructure positioned us as the partner of choice.

Q **What were key factors in making this partnership successful?**

SM It takes a village.

GS In addition to development sponsor and device developer, there was buy-in from primary container component suppliers, CMOs and filling equipment manufacturers. It was a situation where there was a convergence and alignment of interests. Several syringe suppliers, who may have been left out of the microlitre dosing space, looked at the MDS as an enabling technology. A syringe that typically delivers millilitre doses can now deliver accurately and precisely a microlitre dose. Figure 3 shows results from a study in which ophthalmologists attempted to deliver a 50 µL dose using the MDS and conventional prefilled syringes, and which demonstrates how effective the MDS is in improving dosing accuracy.

In addition, the Santen team delegated a lot of decision making to Congruence, which was very important to move the device development fast. The Santen team's integrated approach included involvement in all aspects of drug fill-finish tasks even if it did not involve a device component. This ensured that decisions in the drug fill-finish process did not blindside the device development team.

Q **What's next for the MDS?**

SM This platform could help us get products into human trials with very minimal dosing as there are not many options for filling at the time of use for low-volume filling. It can also reduce cost of expensive modalities with low fill-volumes, and improve shelf-life stability where vial headspace is not desired.

GS The MDS platform can be made available as a prefilled syringe format or so that drug can be filled from a vial, and its injection dose volume can be preset by the manufacturer, or set by the user. This gives four different combinations of configurations (Figure 4). The MDS in its non-prefilled configuration enables a prefillable syringe to be paired with a vial-filled drug. We have initiated submission of the MDS for US FDA 510k premarket clearance. expect in 2020 the MDS will be available for use in drug clinical trials or drug commercial sales.

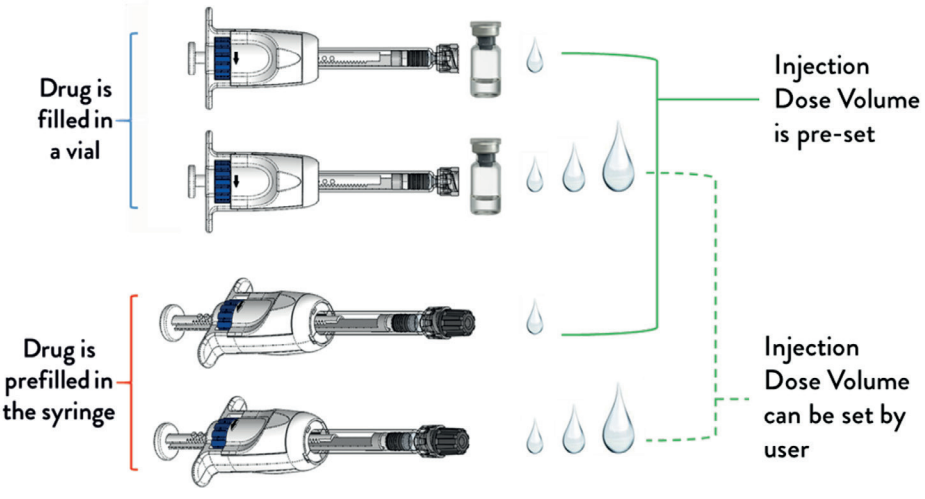

Figure 4: The MDS platform can be made available in four different configurations.

ABOUT THE COMPANIES

Santen Pharmaceutical, established in 1890, is a global company in the business of research, development, production and marketing of pharmaceuticals and medical devices focused in the ophthalmic field. By focusing on ophthalmology, Santen develops unique scientific knowledge and organisational capabilities that contribute to the wellbeing of patients, their loved ones and consequently to society. Headquartered in Osaka, Japan, Santen has 4,073 employees worldwide.

Congruence Medical Solutions is a science-based, technical innovation company focused on the development and supply of ophthalmic drug delivery devices. Its main product is a device for the delivery of accurate, precise microlitre intra-ocular doses using standard prefillable syringes.

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OPTIMISING OPHTHALMIC DRUG DELIVERY FOR THERAPEUTIC EFFECTIVENESS

In this article, Barbara Morgan, PhD, General Manager of CDMO Services at Lubrizol Life Science Heath, offers a fresh take on one of today's most challenging ophthalmic drug delivery issues as well as trends in the industry. She discusses how eye physiology impacts product formulation and choice of dosage form, and how advanced delivery technologies are providing new options for formulators seeking to improve the bioavailability or stability of their ophthalmic treatments.

Delivery of therapeutics to the human eye is one of the more challenging projects a drug developer can take on. The anatomy and chemical composition of the eye make it highly resistant to pharmaceutical penetration. Successfully circumventing these protective barriers requires extensive knowledge and experience of ocular drug delivery, as well as specialised formulation, development and manufacturing expertise.

TRENDING TOWARDS COMPLEXITY

Dosage form options are diverse, ranging from topical emulsions, suspension, and solutions to injectables and implants, as are the formulation options and delivery considerations for each.

Pharma innovators across the board are increasingly engaging outsourced service providers to develop and manufacture their ophthalmic formulations. This is largely due to the fact that complex formulations and dosage forms – such as long-acting intravitreal injections and biodegradable ocular implants – have become increasingly prevalent. Additionally, overall trends in healthcare and the pharma industry are prompting development of increasingly potent and hard-to-manufacture formulations. The advanced expertise and equipment required for these products has made in-house development more challenging.

> "The ocular pharma industry is experiencing an unprecedented surge in venture capital investment, innovation and new drug and biologic approvals."

INCREASE IN DRUG APPROVALS

The ocular pharma industry is experiencing an unprecedented surge in venture capital investment, innovation and new drug and biologic approvals, facilitated by a fundamental shift in how the US FDA handles new drug applications.

In 2012, the FDA Safety and Innovation Act (FDASIA) was enacted, creating the "breakthrough therapy" designation to identify promising new drugs and boost their development.[1] The programme is proving to be quite successful – in 2018, the FDA approved 61 novel drugs.[2] For ophthalmics, in particular, between 2015 and 2018 there was an 800% increase in new ocular drug approvals. In addition, in 2017, two novel therapies for glaucoma were approved – an indication that had not seen a new treatment option for more than 20 years.[3] Only a few months later, the first-ever gene therapy for ophthalmic use was approved to treat mutation-associated retinal dystrophy.[4]

> "Between 2015 and 2018 there was an 800% increase in new ocular drug approvals. In addition, in 2017, two novel therapies for glaucoma were approved – an indication that had not seen a new treatment option for more than 20 years."

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"Obstacles experienced in some standard ocular drug products have led many to investigate alternative drug delivery systems."

TOPICALS FOR THE FRONT OF THE EYE

Ocular drug delivery is classified into two categories – posterior and anterior – each of which possesses unique barriers. Anterior drug delivery focuses primarily on penetrating the cornea, which is commonly targeted with topical solutions, suspensions and emulsions in the form of drops, gels or ointments. Topical drug administration has been the standard of care in ophthalmics for decades, yet it still presents challenges formulators have not fully overcome. For instance, only 1-5% of a topically administered drug is absorbed at the site of action.[5]

Permeating the cornea is challenging because of several precorneal loss factors, including lacrimation (tearing), solution drainage, blinking and non-productive absorption in areas that are not the target tissue. As a result, more frequent dosing is often required, which is wasteful of the drug or may result in side effects.

POSTERIOR OCULAR DRUG DELIVERY

Posterior drug delivery refers to the back segment of the eye, which consists of the choroid, vitreous and retina. The retina, in particular, is a primary focus of many posterior treatments and comprises a thin layer of tissue critical for sight. The back of the eye is considered one of the most difficult areas to treat effectively. The posterior segment is generally inaccessible via topical routes due to the natural impermeability of the eye's exterior and the time and distance therapeutic agents would have to travel to reach the site of action.

Systemic delivery via oral or intravenous administration is also not practical for treating the posterior segment. High concentrations of the drug need to be in the bloodstream for it to pass through the retinal artery and achieve efficacious levels inside the eye. Despite these shortcomings, more than 90% of ophthalmic therapeutics on the market in 2010 were topical.[5]

Obstacles experienced in some standard ocular drug products have led many to investigate alternative drug delivery systems. Back-of-the-eye drug developers are increasingly turning to controlled or sustained release systems, such as implants, drug-eluting particulates and injections into the vitreous or closely surrounding tissue. These dosage forms incorporate additional technologies that facilitate effective drug release.

OPHTHALMIC INJECTABLES

Liposomes and Particulates

One controlled release approach that can help contain potent APIs involves combining a drug with lipid vesicles, known as liposomes. Liposomes consist of a phospholipid bilayer, which is naturally attracted to cell membranes and can therefore bind easily to facilitate effective drug transfer when loaded with an API. They have the unique advantage of being able to deliver both hydrophobic and hydrophilic drugs.

Micro and Nano Particulates

Another delivery approach combines drug with a polymeric compound to form micro- or nanoparticulates. These can be of a reservoir or matrix composition, meaning a drug is either encapsulated within or distributed evenly throughout a polymer. One of the most commonly investigated polymers for this application is polylactic-co-glycolic acid due to its ability to break down safely in the body and release drug at a controlled rate when injected.

Particle size reduction has proven to successfully aid in delivering drugs because it increases the surface area for the API to be exposed for absorption by adjacent tissues.

OCULAR IMPLANTS

Ocular implants are often inserted into the vitreous humour, the suprachoroidal space or the closely surrounding tissue and have been developed in both biodegradable and non-biodegradable forms. They can sustain localised drug delivery for up to several years. The advantage of sustained release has caused the development of ocular implants to gain significant momentum in recent years.

Ocular implants make up approximately one-third of all FDA-approved implants on the market with numerous additional products hot on their heels in clinical development. They have been found effective in the treatment of several retinal disorders, where sustained release is key. Retinal disorders are typically considered treatable but not curable – meaning, once developed, these conditions will require ongoing care.

ABOUT THE COMPANY

The health business team at Lubrizol Life Science partners with customers to speed their innovative medical devices and differentiated pharma products to market. Its team provides high-quality polymers and excipients, along with state-of-the-art product design, development and manufacturing services, with the ultimate goal of creating solutions that improve patient outcomes.

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ABOUT THE AUTHOR

Barbara Morgan has worked with LLS Health, a Lubrizol Life Science Company, since 2014 and was named General Manager in 2018. In addition, she has a larger global role serving as the Global Business Director for all of Lubrizol Life Science's pharma businesses, facilitating a strong relationship between the different business units. With a PhD in Organic Chemistry from the University of Pennsylvania (US), Dr Morgan has more than 15 years' experience in both drug development and business development in the pharma industry. She has published numerous articles in peer-reviewed journals and holds patents, including one on the treatment of cancer stem cells.

ON drugDELIVERY

2020/21 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
April 2020	Pulmonary & Nasal Drug Delivery	Mar 5, 2020
May 2020	Injectable Drug Delivery: Formulations & Devices	Apr 2, 2020
June 2020	Connecting Drug Delivery	May 7, 2020
July 2020	Novel Oral Delivery Systems	Jun 4, 2020
August 2020	Industrialising Drug Delivery	Jul 2, 2020
September 2020	Wearable Injectors	Aug 6, 2020
October 2020	Prefilled Syringes & Injection Devices	Sep 3, 2020
November 2020	Pulmonary & Nasal Drug Delivery	Oct 1, 2020
December 2020	Connecting Drug Delivery	Nov 5, 2020
January 2021	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 3, 2020
February 2021	Prefilled Syringes & Injection Devices	Jan 7, 2021
March 2021	Ophthalmic Drug Delivery	Feb 4, 2021

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