# OPHTHALMIC DRUG DELIVERY

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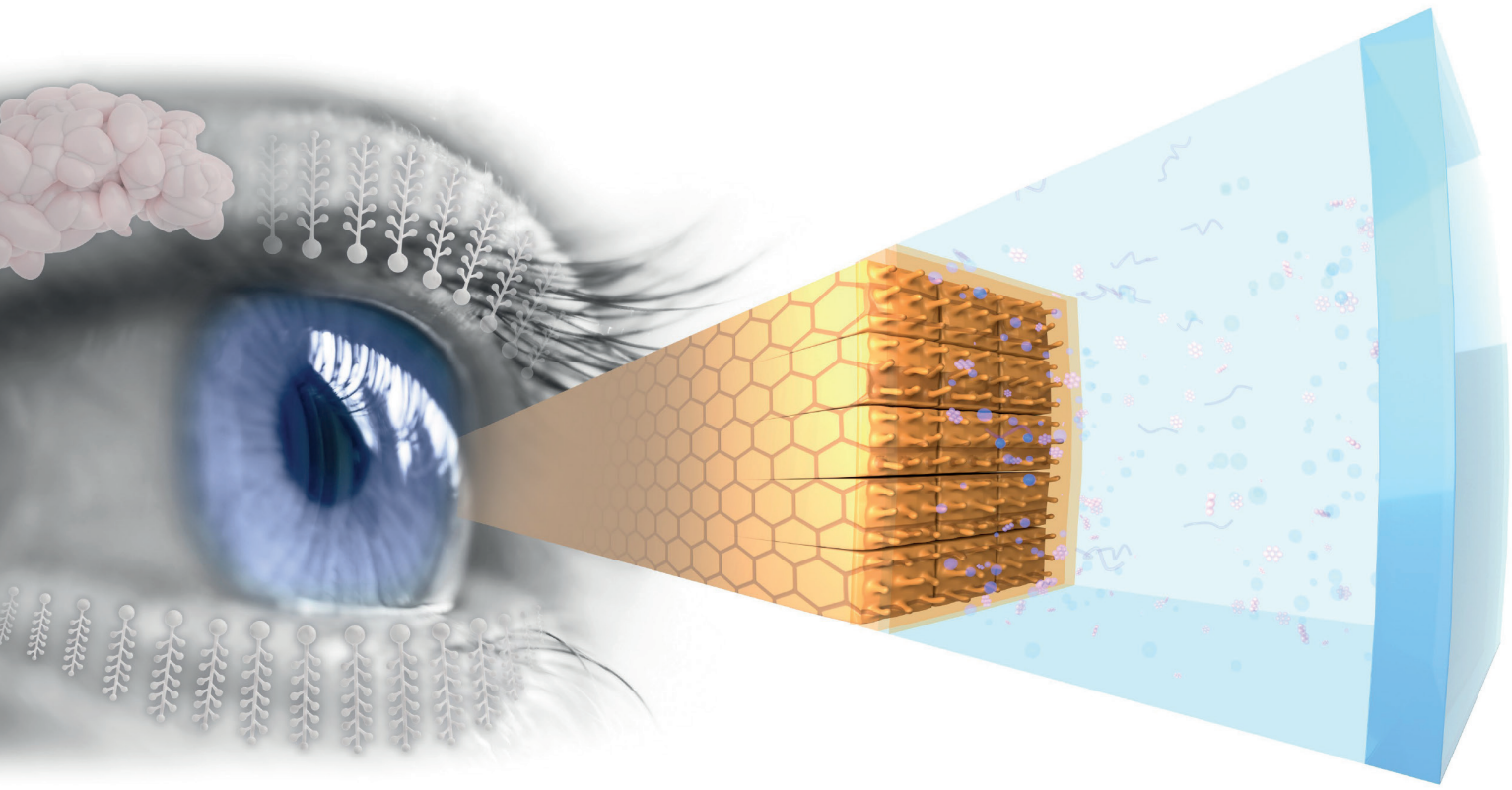

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## OPHTHALMIC DRUG DELIVERY

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### EDITORIAL:

Guy Furness, Proprietor & Publisher
T: +44 1273 47 28 28
E: guy.furness@ondrugdelivery.com

James Arnold, Assistant Editor
T: +44 1273 47 28 28
E: james.arnold@ondrugdelivery.com

### SUBSCRIPTIONS:

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### ADVERTISING:

Guy Furness, Proprietor & Publisher
T: +44 1273 47 28 28
E: guy.furness@ondrugdelivery.com

### MAILING ADDRESS:

Frederick Furness Publishing Ltd
The Candlemakers, West Street, Lewes
East Sussex, BN7 2NZ, United Kingdom

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*Front cover image, "human tear film with glands", supplied by Novaliq (see this issue, pp 14-18). Reproduced with kind permission.*

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| February 2019 | Prefilled Syringes & Injection Devices | PASSED |
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| June 2019 | Connecting Drug Delivery | May 2nd 2019 |
| July 2019 | Novel Oral Delivery Systems | Jun 6th 2019 |
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| December 2019 | Connecting Drug Delivery | Nov 7th 2019 |
| January 2020 | Ophthalmic Drug Delivery | Dec 5th 2019 |

# THE CHALLENGES AND OPPORTUNITIES OF DRUG DELIVERY THROUGH A COMPLEX BARRIER

In this article, Jon Volmer, PhD, Director of Research Biology, Marc Brown, PhD, Chief Scientific Officer and Co-founder, and Jeremy Drummond, PhD, Senior Vice-President, Business Development, all of MedPharm, discuss the development and use of advanced *ex vivo* and *in vitro* models for testing new ocular medicines to meet a growing unmet need.

## INTRODUCTION

The prevention and treatment of diseases of the eye represents a US$23 billion (£18.2 billion) annual market globally.[1] The major impact eye health and vision make on quality of life means that this is a rewarding area for development of any drug products that meet a medical need. Modern lifestyles and an ageing population are also bringing the need for solutions to ocular diseases, such as dry eye disease (DED), to the attention of the ophthalmology community. The pharmaceutical industry has responded to this and there are currently over 2,500 clinical trials underway related to ocular drug products.[2] This number is being boosted by a greater understanding of basic biology in other therapeutic areas, which is uncovering overlaps with certain pathways and targets in the eye, especially in immunology and inflammation.

> "To be able to formulate a topical eye product successfully, it is fundamental to understand the complex, multilayered nature of the surface of the eye."

As a distinct organ with easy access, the eye is ideal for direct drug delivery. This can be achieved topically or by either intravitreal or trans-scleral injection. From the patient perspective, any drug with the possibility of being delivered topically will be preferable to an injection that must be performed by an appropriate healthcare professional (HCP).

Ocular delivery presents both unique challenges and opportunities due to the eye's structure and function. To be able to formulate a topical eye product successfully, it is fundamental to understand the complex, multilayered nature of the surface of the eye. This understanding can be greatly enhanced by an ability to create relevant and meaningful models of this unique barrier in order to select the appropriate drugs and optimise formulations within the laboratory. Such knowledge gives a product

> "For MedPharm and its clients, *in vitro* and *ex vivo* models have proven themselves invaluable for optimising topical drug formulations and de-risking development programmes."

**Dr Jon Volmer**
Director of Research Biology

**Prof Marc Brown**
Chief Scientific Officer and Co-founder

**Dr Jeremy Drummond**
Senior Vice-President,
Business Development
E: busdev@medpharm.com

**MedPharm Ltd**
Global HQ
Unit 1 Chancellor Court
50 Occam Road
Guildford
GU2 7AB
United Kingdom

**www.medpharm.com**

the best chance of providing positive health benefits to the patient.

## THE DRUG DELIVERY CHALLENGE

An understanding of the structure of the eye surface barrier is crucial to understanding how a drug is likely to reach its site of action (Figure 1).

The first barrier on the surface of the eye comprises the glycocalyx, which are long chain molecules that help hold mucin to the corneal surface. Formed by corneal cells, glycocalyx migrate out from the surface of the corneal microvilli to form a hydrophilic network that holds mucin on the ocular surface. The glycocalyx is a well-ordered gel layer, extending 200–500 nm above the corneal epithelium.[3] Although it is thought that the primary function of this layer is to maintain hydration and lubrication of the corneal surface, it also presents a significant barrier to drug delivery, as water binding and displacement by the glycocalyx can have significant impact on effective concentrations and gradients. The glycocalyx can also potentially be exploited as a depot platform to retaining drug near the corneal epithelium.

Below the glycocalyx lies the cornea itself, comprising three distinct layers, the epithelium, the stroma and the endothelium. The epithelium presents a significant barrier because of its lipophilic nature and extensive tight junctions, which closely link the cells and therefore leave little space for diffusion between them. Corneal epithelial cells also express an array of ATP-binding cassette efflux transporter pumps. These pumps actively remove lipophilic molecules, organic anions and conjugated compounds from the cytoplasm of corneal epithelial cells. They represent one of the most active elements of the corneal barrier and as such ideally need to be avoided when optimising drug delivery. Corneal epithelial cells have also been shown to express an array of solute-linked carrier (SLC) influx transporter pumps, which actively bring in nutrients and signalling molecules, making them a tempting target for drug delivery to the corneal epithelium.[4] There is also evidence that corneal epithelial cells have the potential to phagocytose particulates from the tear film.[5]

Below the corneal epithelium is the stroma, which is comprised of highly structured collagen lamellae, several hundred micrometres thick (comprising almost 90% of the thickness of the cornea)

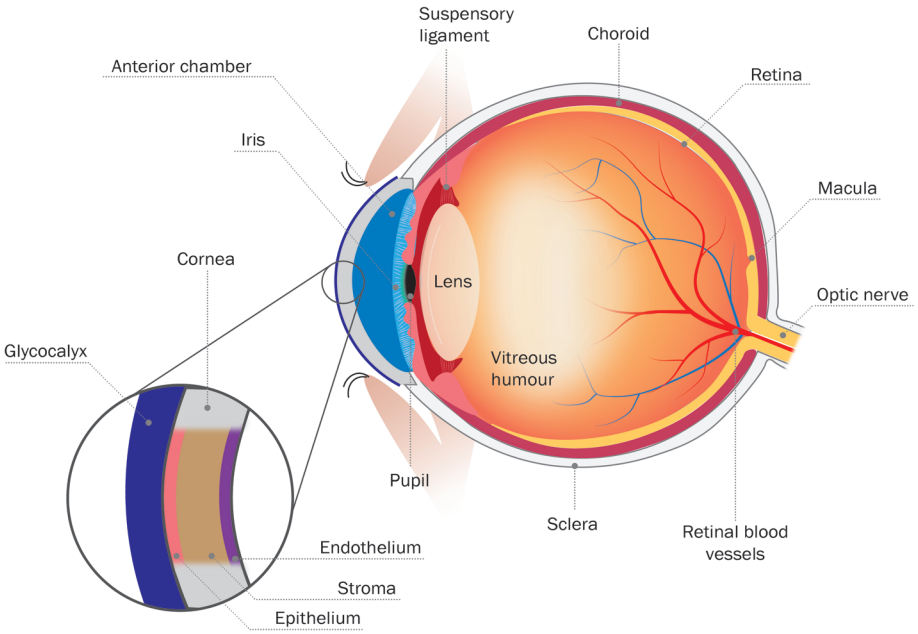


Figure 1: Schematic diagram of eye and corneal barrier.

and highly hydrophilic. Whilst lipophilic drugs are preferable for permeation through the corneal epithelium, hydrophilic drugs are preferred for permeation through the stroma. This can be exploited in drug structure optimisation, depending on which compartment is being targeted.

The final layer of the cornea is the endothelial layer, separating the stroma from the anterior segment of the eye. The leaky nature of cell-cell interactions at the endothelium means it represents minimal function as a barrier.

The eye, in a similar way to any external surface on the body, has evolved to prevent intrusion by foreign molecules and particles. However, an influx of inflammatory cells and vascularisation, as seen with other barriers such as the skin, are not an effective early response mechanism for the eye due to the fact that the cornea must remain transparent. Thus, the compact surface barrier of the cornea and sclera is complimented with a protective stream of tears and the regular sweeping of the eyelid. This makes topical drug delivery to the eye a significant challenge.

When a formulation is applied to the surface of the eye, clearance of the product is immediately initiated. The normal tear volume on the surface of the human eye is approximately 7 µL, and the exposed surface of the eye can typically hold a maximum of about 30 µL before overflowing. This limits any useful topical application to around 23 µL. Tear volume usually reverts to normal within 2–3 minutes. In addition, the blink response can amplify this clearance dramatically. It can result in a total contact time of the drug with the absorptive surface of the eye of five minutes or less.[6]

This leaves much room for improvement through the selection of drugs with permeation properties specific to the barriers present in the eye and the design and development of optimised bio-adhesive formulations. Appropriate *in vitro* and *ex vivo* models are therefore a critical tool in topical product development for the eye.

## EFFECTIVE MODELS FOR DRUG DELIVERY TO THE EYE

For MedPharm and its clients, *in vitro* and *ex vivo* models have proven themselves invaluable for optimising topical drug formulations and de-risking development programmes because they provide a strong indicator of the likely performance in the clinic, and models of the eye continue to gain in sophistication.

Prior to any drug penetration or permeation taking place, it is important to maximise the opportunity for a formulated drug to get to the surface of the eye and bind against the flow of tears. For many years, MedPharm has used *ex vivo* models in which the level of adhesion to corneal tissue is measured whilst the surface is perfused with artificial tear fluid at a defined rate. In MedPharm's testing approach, the drug release from the formulation and the residency time of the formulation on the eye are maximised in parallel to maintaining chemical and physical drug stability, thus providing the best chance of success. In

order to mitigate the risk of failure, a wide range of excipients (including but not limited to penetration enhancers and bio-adhesive agents) need to be tested in numerous formulations.

These *in vitro* and *ex vivo* models help to characterise and optimise formulations in pursuit of increasing their residency time in the presence of tear fluid, whilst limiting vision impairment, in a cost-effective and efficient manner. This also negates the need for performing relatively expensive *in vivo* studies in animals at an early stage. These models can be used to screen larger numbers of formulations than animal studies. Typically, MedPharm develops the adhesion models for a specific drug compound using the appropriate *ex vivo* animal eyes. The use of human corneal tissue, sourced from cadavers, is restricted to *in vitro* permeation and penetration testing and disease models.

MedPharm use corneal tissue for assessing vehicle and formulation effects on the penetration and permeation of a drug into and across the cornea using modified static and validated diffusion cells. Animal corneal tissue is used during method development and then final experiments are carried out using human corneal tissue. These experiments give a good idea of the likely challenges for a drug's delivery and any concentration build up in a particular layer of the cornea can be identified.

Whether from humans or animals, these models have the benefit of using real corneal tissue, possessing all of the gross anatomical characteristics. Care must be taken in interpreting results from these studies, as some of the barrier function in the cornea is due to active processes. Treatment during harvest, storage, transportation and processing of the cornea is likely to result in damage or degradation of the tight junctions of the corneal epithelium. While the integrity of the tissue can be screened prior to experimentation by measuring transepithelial resistance, other less easily detected damage may also occur. The glycocalyx can be sloughed or damaged and efflux/influx transporters will be functionally lost. When using models of this type MedPharm recognises the need for fast and careful preparation and also careful interpretation of results in the knowledge that some drugs may behave differently in more viable eye tissue.

> "The combination of tissue culture and human/animal eye models for the evaluation and optimisation of drug/formulation retention, drug permeation and penetration, and disease activity provides a powerful toolkit for ocular drug product development."

For obvious reasons, there is not a readily available supply of fresh, healthy eye tissue. Biologists at MedPharm are increasingly relying on tissue culture models based on primary corneal epithelial cells from healthy rabbits, as well as commercially available human sources, to form a functional, well differentiated epithelium as an appropriate replacement.

For these models, the cells are grown in transwells (Figure 2) on a membrane supported on the surface of cell culture media. Cells are in contact with media on the basolateral side and exposed to air on the apical side. As in many epithelial tissues, this polarised culture condition promotes the formation of tight junctions, production of appropriate mucins or other surface proteins, and the establishment of a barrier very similar to the natural barrier offered by an intact corneal epithelium. Cells grown in this fashion exhibit transepithelial resistance similar to that of native corneal tissue, which strongly suggests that functional tight junctions are present.[7] Furthermore, these models have the potential to express a functional glycocalyx and an appropriate efflux/influx transporter system. Additionally, expression of the appropriate genes has been observed at the transcript level. These models can also be used to assess drug activity by upregulating key disease biomarkers. They offer the formulator the key benefit of being a cost-effective and readily available way of optimising a product by allowing the relatively rapid testing of multiple drugs and formulations.

There are also models available for corneal tissue based on immortalised human corneal epithelial cells. MedPharm's preference is not to use these models because they can undergo significant metabolic changes through the transformation process needed to maintain long-term viability. These changes can result in a significant depletion in integrity as measured by trans-epithelial resistivity compared with primary cell cultures, which will have a significant impact on the ability of a drug to permeate and penetrate the tissue.

More recently, MedPharm has developed a set of tissue culture and human/animal eye models for various diseases. These enable its clients to screen their drugs and/or formulations against eye conditions such as DED, infections and inflammatory conditions (for example conjunctivitis, keratitis, uveitis and blepharitis). These models are disease and drug specific and allow for comparison of the activity a new drug/formulation with those already marketed.

MedPharm continues to develop novel eye delivery models to support its customers' ocular product developments. Changes in media and culture conditions

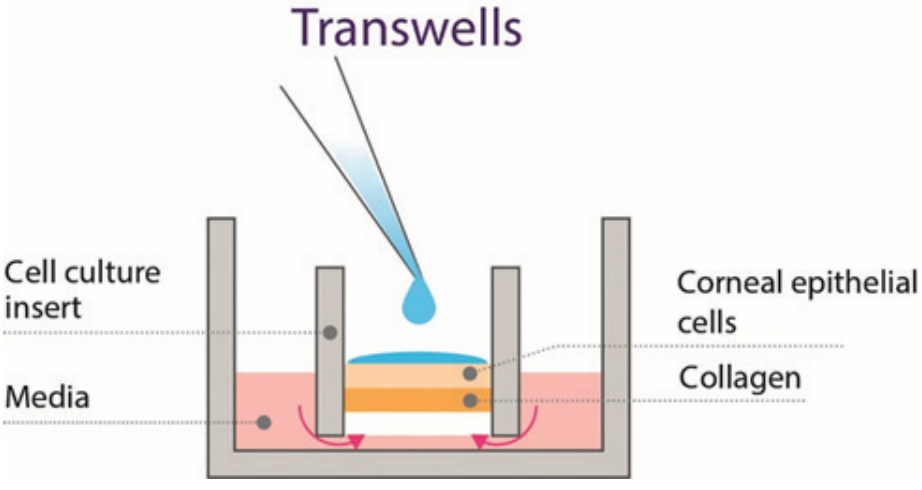


Figure 2: Diagram of a transwell.

continue to lead to even greater alignment to the native eye tissue. The combination of tissue culture and human/animal eye models for the evaluation and optimisation of drug/formulation retention, drug permeation and penetration, and disease activity provides a powerful toolkit for ocular drug product development. The next step is to combine these more sophisticated biological models with physical components, such as tissue clearance in a single eye model.

## CONCLUSION

The unique nature of the epithelial barrier in the eye presents a significant challenge in the development of effective treatments for ocular diseases. The development and use of increasingly relevant *in vitro* and *ex vivo* models reduces the risks associated with this challenge. These models can be used as a cost-effective screen for selecting drug candidates and identifying the optimal formulation prior to any significant investment in their development. They offer significant advantages over *in vivo* animal models when there is a need to test large numbers of formulations. The demand for ocular pharmaceuticals to meet current unmet medical needs will undoubtedly continue to increase, and these models will play a key role in reducing the risks, costs and timelines associated with any such development.

## ABOUT THE COMPANY

MedPharm is a leading global provider of contract topical and transdermal product design and formulation development services. MedPharm is expert at reducing risk and accelerating development times for generic and proprietary pharmaceutical customers through the use of proprietary, industry-leading performance testing models. Well-established in dermatology, nail, mucosal membrane and transdermal product development, MedPharm also offers innovative solutions for ophthalmic and airway preparations. These solutions are recognised for their scientific rigour by regulators and investors. MedPharm has fully established R&D centres in the US and UK and GMP clinical manufacturing capabilities at its global headquarters facility in Guildford, UK.

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## ABOUT THE AUTHORS


**Jon Volmer** joined MedPharm in 2016 to generate new technologies, systems and biological models, and expand MedPharm's capabilities serving the needs of current clients, and expand into new areas of expertise. He has more than 15 years' experience developing a variety of biological models and technological lab support equipment in fields including immunology, microbiology, pulmonary disease, and mechanical modeling. Dr Volmer received his PhD on the biochemical basis of inflammatory remodeling in the lung from the University of Texas Graduate School of Biomedical Sciences (TX, US).

**Prof Marc Brown** co-founded MedPharm in August 1999 and has been the guiding force behind all the company's scientific developments and intellectual property. He has been Professor of Pharmaceutics at the School of Pharmacy, University of Hertfordshire, since 2006 and has honorary professorships at the University of Reading and King's College London. Prof Brown has over 200 publications and 26 patents describing his work. His research interests lie mainly in drug delivery to the skin, nail and airways. To date, he has been involved in the pharmaceutical development of over 38 products that are now on the market in Europe, America and Japan.

**Dr Jeremy Drummond** joined MedPharm in February 2017. He has spent over 20 years leading the commercial supply of product and services to the pharmaceutical companies across the globe. He is responsible for leading revenue growth, key client relationships and marketing MedPharm to its global customer base. He started his career as a technical formulator and has a PhD in organic chemistry from the University of Cambridge.

# TARGETING DRUGS TO DISEASED OCULAR CELLS

In this article, Frazer Coutinho, PhD Candidate, Colin Green, PhD, W&B Hadden Chair of Ophthalmology & Translational Vision Research, and Ilva Rupenthal, PhD, Senior Lecturer and Director of the Buchanan Ocular Therapeutics Unit, all of the University of Auckland's Department of Ophthalmology, discuss the targeted delivery of ocular therapeutics to diseased cells, using the cell-penetrating peptide, Xentry.

## OVERCOMING THE BARRIERS TO EFFICIENT OCULAR DRUG DELIVERY

### Ocular Barriers

The eye is a complex organ with multiple tissue layers that create anatomical and physiological barriers in order to protect it from the environment. These barriers include the cornea and sclera on the exterior while the inner limiting membrane (ILM) protects the retina on the interior. As a result, ocular drug delivery, especially to retinal cells, has long been a significant challenge. For example, drugs delivered orally or systemically have to be administered at very high concentrations in order to achieve a therapeutic effect at the target site. Even drugs delivered locally, in the form of eyedrops or intravitreal injections, face a number of barriers and elimination mechanisms necessitating the use of high drug concentrations to improve efficacy. The off-target effects resulting from such high drug concentrations can then create additional challenges, often resulting in secondary complications.

### Improving Ocular Drug Delivery

Multiple approaches, including ultrasound, penetration enhancers and colloidal carriers such as nanoparticles and liposomes, have been developed in order to improve ocular drug delivery. While these systems may deliver the drug closer to its site of action, they are generally not targeted specifically to injured cells, with the cellular uptake of intracellularly acting molecules (siRNA, peptides, small molecules) also being limited. Cell-penetrating peptides (CPPs) can transport their cargo across the cell membrane in a biologically active and bioavailable form.[1] Well-established CPPs explored for ocular drug delivery include the transactivator of transcription (TAT) and penetratin, as well as newer CPPs, such as the peptide for ocular drug delivery (POD).[1] However, while most CPPs transport their cargo into cells, they are non-cell-specific, often delivering drugs into multiple cell types. This lack of specificity reduces the therapeutic dose in the target cells while also increasing the potential for off-target effects.

## CPPS FOR TARGETED OCULAR DRUG DELIVERY

### Xentry

Xentry is a short CPP (seven amino acids) which has been used to transport a range of cargo molecules into cells, including siRNA, oligonucleotides and antibodies.[2] Xentry is unique compared with most other CPPs, as it only enters Syndecan-4 expressing cells. Therefore, Xentry does not enter cells such as non-adherent monocytes and erythrocytes, which makes it ideal for systemic administration as it is not sequestered by the blood circulation. Furthermore, by specifically targeting Syndean-4 expressing cells and initiating rapid uptake, Xentry and its conjugated cargo can evade degradation by enzymes in the serum, allowing the overall administered dose to be reduced.

> "Xentry is unique compared with most other CPPs, as it only enters Syndecan-4 expressing cells. Therefore, Xentry does not enter cells such as non adherent monocytes and erythrocytes, which makes it ideal for systemic administration."

### The Functions of Syndecan-4

Syndecans are a family of transmembrane heparan

**Frazer P Coutinho**
PhD candidate
T: +64 9 923 6471
E: f.coutinho@auckland.ac.nz

**Prof Colin R Green**
W&B Hadden Chair of Ophthalmology & Translational Vision Research
T: +64 9 923 6135
E: c.green@auckland.ac.nz

**Dr Ilva D Rupenthal**
Senior Lecturer and Director of BOTU
T: +64 9 923 6386
E: i.rupenthal@auckland.ac.nz

**Buchanan Ocular Therapeutics Unit**
Department of Ophthalmology
New Zealand National Eye Centre
University of Auckland,
Private Bag 92019
Auckland 1142
New Zealand

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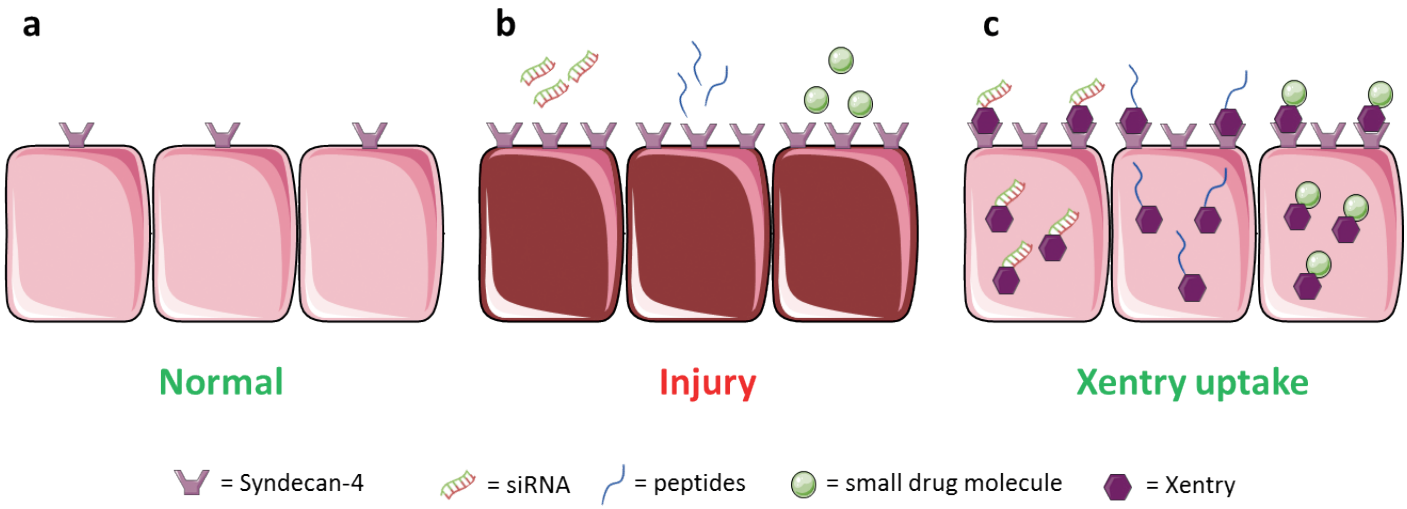


Figure 1: Xentry targets increased Syndecan-4 expression in injured cells. (a) Under normal conditions, cells express low levels of Syndecan-4. (b) During injury, Syndecan-4 levels are upregulated; however, untargeted therapeutics are unable to enter cells efficiently. (c) Conjugation of the therapeutic to Xentry enables specific targeting and increased uptake into Syndecan-4 overexpressing injured cells.

sulphate proteoglycans, with four syndecans having been identified in mammalian cells so far.[3] Low levels of Syndecan-4 are present in many different cell types under normal conditions, mediating numerous signalling pathways including proliferation, migration and endocytosis. Syndecan-4 binds multiple molecules such as fibronectin, integrin and paxillin for the formation of focal adhesions, as well as biochemical signalling by binding extracellular growth factors, including vascular endothelial growth factor (VEGF).[3] Most importantly, Syndecan-4 has been shown to be overexpressed in diseased cells.

### Targeting Syndecan-4 with Xentry in Ocular Disease

In diseased ocular tissues, increased Syndecan-4 expression results in the binding of proteins such as VEGF in order to enhance interactions with the VEGF receptor, therefore stimulating blood vessel growth.[3] Consequently, there is potential to specifically target diseased cells that overexpress Syndecan-4 by using the CPP Xentry (Figure 1).

Recently, we have discovered that cultured retinal pigment epithelial cells and retinal microvascular endothelial cells increase cell-surface expression of Syndecan-4 under hypoxic, inflammatory and hyperglycaemic conditions. Human age-related macular degeneration (AMD) and diabetic retinopathy (DR) donor tissues also exhibited increased Syndecan-4 expression, primarily around large leaky blood vessels in the retina. Interestingly, the ILM of donor retinas, which contains astrocytic endfeet, also showed strong Syndecan-4 labelling. The ILM has long been a barrier to efficient drug delivery into the retina. Recently, astrocytic endfeet have been proposed as a way of delivering drugs across the ILM and further into the retina utilising astrocytic processes. Thus, higher Syndecan-4 expression on astrocytic endfeet in the ILM provides yet another opportunity for more efficient drug delivery into the retina when the therapeutic is injected intravitreally.

> "XG19 is a novel peptide therapeutic that specifically targets diseased cells in order to reduce inflammation and promote cell survival."

## XG19 AS A NOVEL THERAPEUTIC FOR AMD

### What is XG19?

XG19 is a novel peptide therapeutic that specifically targets diseased cells in order to reduce inflammation and promote cell survival. When used in ocular disease, XG19 promotes the survival of endothelial cells and repairs blood vessels, thus reducing vascular leak and inflammatory mediator concentrations in the environment. The repair of blood vessels also restores the normal blood supply to the tissues which helps to address the underlying ischaemia. Overall, XG19 restores and maintains blood-retinal barrier integrity by targeting both the hypoxic retinal pigment epithelium and the leaky blood vessels (Figure 2).

### How Could XG19 Be Used Therapeutically?

Our group has studied biochemical changes and protein expression in a number of ocular diseases. Of the multitude of proteins elevated, Connexin43 (Cx43) is one that stands out. A number of studies have shown that blocking Cx43 hemichannels in inflammatory or hypoxic disease results in increased cell survival and tissue repair. This is particularly useful for vascular eye diseases, such as AMD and DR, where the blood supply is compromised and requires restoration.[4] Gap19 is an intracellularly acting Cx43 hemichannel blocker. However, the native peptide has low cell permeability, necessitating the administration of high doses in order to achieve a therapeutic effect.[5] To improve cell penetration and specifically target injured Syndecan-4 expressing retinal cells, Gap19 was conjugated to Xentry and was given the name XG19.

Our *in vitro* studies showed that XG19 uptake was greatly increased during hypoxic, inflammatory and hyperglycaemic conditions due to increased Syndecan-4 expression, confirming that XG19 could be primarily targeted to injured retinal cells. XG19 was able to specifically block uncontrolled Cx43 hemichannel opening in injured cells, inhibiting ATP release as well as increasing cell survival at concentrations as low as 5 µM, which is much lower than concentrations of native Gap19 (300 µM) used in similar assays.[5] This highlights that Xentry is able to improve the specificity and thus delivery of bioavailable Gap19 into injured cells.

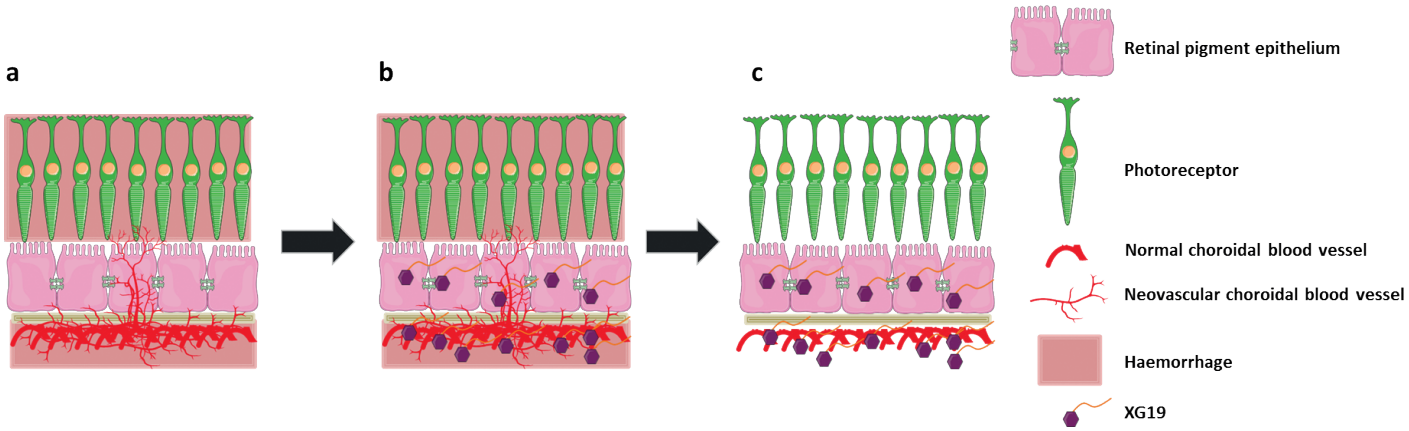


Figure 2: Therapeutic potential of XG19 in neovascular AMD. (a) Chronic unregulated blood vessel growth in the choroid (choroidal neovascularisation) results in poorly formed and leaky vessels. This disrupts the vascular supply leading to tissue ischaemia, hypoxia and inflammation. Retinal pigment epithelial cell death eventually disrupts the blood-retinal barrier and permits blood vessel growth into the sub-retinal space where further haemorrhage leads to vision loss. (b) Administration of Xentry-Gap19 (XG19) results in targeted delivery of the therapeutic peptide (Gap19) to hypoxic retinal pigment epithelial cells and choroidal blood vessels that overexpress Syndecan-4. (c) Efficient Cx43 hemichannel block reduces tissue inflammation and promotes blood vessel repair thus restoring the normal blood supply to the retina.

In an *in vivo* mouse model of choroidal neovascularisation (CNV), in which a laser is used to disrupt the blood-retinal barrier to mimic AMD pathologies, XG19 delivered via a single intraperitoneal injection was able to promote faster healing and reduce inflammation compared with control animals. Ellipsoid volumes of CNV lesions seven days post-laser treatment revealed that XG19 treated animals had significantly smaller lesion volumes, indicative of reduced blood vessel growth and inflammation. Immunohistochemistry of post-mortem tissues showed reduced Cx43, Syndecan-4 and glial fibrillary acidic protein (GFAP) expression levels in XG19 treated animals, indicative of reduced retinal inflammation.

Overall, XG19 can efficiently enter cells, especially during injury conditions, with the delivered cargo retaining its function. While given systemically during our initial studies, intravitreal injection and improved retinal transfer via Syndecan-4 expressing astrocytic endfeet is also possible.

## FUTURE WORK

Our hope is to further develop XG19 as a therapeutic for vascular eye diseases as well as explore Xentry in combination with other intracellularly acting therapeutics to target diseased Syndecan-4 expressing cells of the eye, specifically.

## ABOUT THE ORGANISATION

The Buchanan Ocular Therapeutics Unit (BOTU) aims to translate ocular therapeutic-related scientific research into the clinical setting, whether pharmaceutical, cell or technology based. The BOTU team is developing novel drugs and tailored controlled delivery systems with projects around dry eye, uveitis, glaucoma, diabetic retinopathy and age-related macular degeneration management.

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## ABOUT THE AUTHORS

**Frazer Coutinho** obtained his Bachelor's degree in Biomedical Science and Master's degree in Science majoring in Microbiology and Immunology from the University of Otago. He has been a PhD student within the Buchanan Ocular Therapeutics Unit, University of Auckland, since 2015, investigating the therapeutic potential of XG19 in ocular disease. He has a passion for innovation and is particularly interested in translational science, taking therapeutics from bench to bedside.

**Colin Green** holds the W&B Hadden Chair in Ophthalmology and Translational Vision Research in the Department of Ophthalmology at the University of Auckland. Professor Green's group focuses on cell reprogramming and connexin channel roles in disease, in particular chronic inflammatory diseases such as those affecting the retina. He has co-authored 185 manuscripts and book chapters and is a named inventor on over 255 patents in 29 patent families. He is a co-founder of CoDa Therapeutics (Auckland, NZ) and OcuNexus Therapeutics (US).

**Ilva Rupenthal** is a Senior Lecturer in the Department of Ophthalmology, University of Auckland, and the inaugural Director of the Buchanan Ocular Therapeutics Unit (BOTU), established in 2013. A pharmaceutical scientist by training, Dr Rupenthal's research focusses primarily on the development of novel ocular drug delivery systems. She is an author on over 60 peer-reviewed journal articles and has attracted more than NZ$5.6 million in research funding.

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# BREAKING THE VICIOUS CIRCLE OF DRY EYE DISEASE

In this article, Christian Roesky, PhD, Chief Executive Officer, Novaliq, discusses the underserved condition of dry eye disease, and presents two products in Novaliq's pipeline, based on the company's water-free, preservative-free EyeSol® technology, for the treatment of different types of DED.

## DRY EYE DISEASE IS OFTEN UNDERESTIMATED

Dry eye disease (DED) is a chronic disease, negatively impacting a patient's quality of life in a manner comparable with other chronic diseases.[1] Symptoms of DED, such as feeling of dryness, burning, foreign body sensation or pain, are often quite debilitating. More recently, visual function related symptoms, such as fluctuating vision with blinking, blurred vision and difficulty with reading despite normal visual acuity, are coming into focus as an important and underestimated aspect of the disease.[2] In addition, adverse effects on mental health, such as depression and anxiety, have been observed.[3] DED is a serious disorder that, if left untreated or undertreated, progressively damages the ocular surface and may lead to vision loss due to corneal complications.[4]

> "As many as 5–35% of patients visiting an ophthalmologist report symptoms of DED, making it one of the most common conditions seen by ophthalmic specialists."

As many as 5–35% of patients visiting an ophthalmologist report symptoms of DED, making it one of the most common conditions seen by ophthalmic specialists.[5] In the US, more than 16 million patients are diagnosed with DED,[6] however approximately only 10% are receiving treatment. In the EU the ratio is similar. This significant gap between diagnosed and appropriately treated patients indicates that new DED therapies are needed.

Treatment of DED has traditionally started with artificial tears and topical lubricants. For more moderate to severe cases topical anti-inflammatory medications, including short 2–4 week courses of corticosteroids and longer-term therapies of cyclosporine A and lifitegrast, are used.[7] Tear film instability can induce ocular surface stress and damage, also potentially initiating an inflammatory cascade that generates innate and adaptive immune responses. These immuno-inflammatory responses lead to further ocular surface damage and the development of a self-perpetuating inflammatory cycle.[8]

Current prescription drugs have seen limited market penetration for two reasons:

- Efficacy of current DED treatments is limited while tolerability is low
- Patients often fail to get a satisfactory response.

As DED is a multifactorial disease, identification of the underlying root cause or disease pathogenesis for a specific patient provides valuable mechanistic guidance to develop targeted and effective treatments addressing different categories.

The International Dry Eye Workshop classifies DED into two major categories:[9]

- Aqueous tear deficient (keratoconjunctivitis sicca)
- Evaporative (=tear-lipid deficient).

**Dr Christian Roesky**
Chief Executive Officer
T: +49 6221 502590
E: info@novaliq.com

**Novaliq GmbH**
Im Neuenheimer Feld 515
69120 Heidelberg
Germany

**www.novaliq.com**

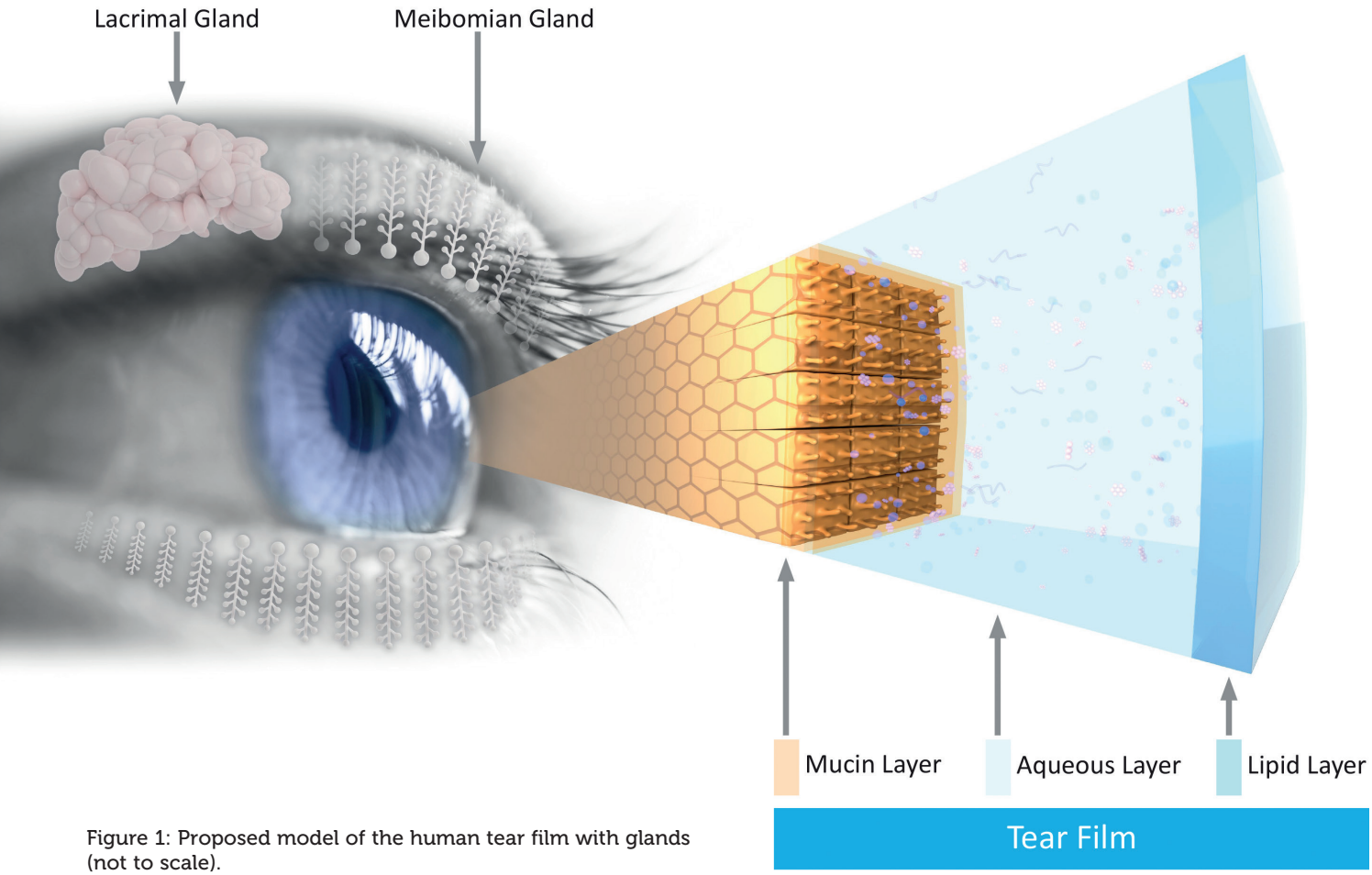


Figure 1: Proposed model of the human tear film with glands (not to scale).

> "Treatment options for patients with evaporative DED are limited, as tear supplementation or anti-inflammatory medications often do not address the underlying root cause of excessive evaporation."

In aqueous-deficient DED, reduced tear production leads to tear film instability. Around 10% of patients with dry eye have a solely aqueous-deficient disorder, and up to 40% have a predominantly aqueous deficiency. In evaporative DED an altered lipid layer leads to tear film instability. The evaporative form of dry eye is more prevalent, 60–90% of patients have predominantly evaporative DED.[10] Meibomian gland dysfunction (MGD) is the leading cause of evaporative DED. Meibum glands play an important role as the main source of lipids for the human tear film. The meibum spreads onto the tear film, promotes its stability and prevents its evaporation.[11,12]

Treatment options for patients with evaporative DED are limited, as tear supplementation or anti-inflammatory medications often do not address the underlying root cause of excessive evaporation. Patients suffering from DED with imbalanced tear conditions due to significant MGD represent a large population with high unmet medical needs in today's clinical care.

This mechanistic understanding of the tear film layers and gland interaction (Figure 1), together with new treatment strategies has led to the modified "vicious circle of DED" (Figure 2), highlighting the pathology and key drivers of the disease.[13]

## OVERCOMING THE LIMITATIONS OF WATER-BASED EYEDROPS

Recently, data has emerged from two clinical trials of novel topical drugs utilising a non-aqueous, preservative-free technology

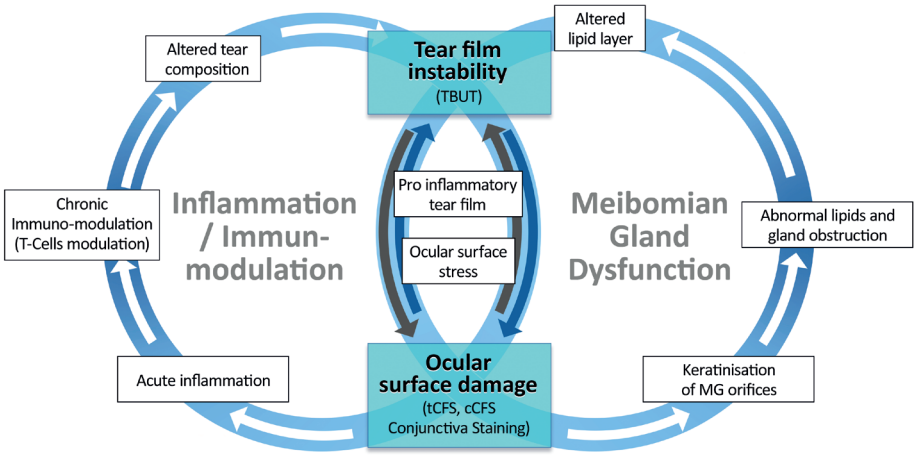


Figure 2: The modified vicious circle of dry eye disease.

that may offer new and promising treatment approaches to improve the quality of life for DED patients in both segments of the disease.

Novaliq is focusing on the development of first- and best-in-class ocular therapeutics based on EyeSol®. As the world's first water-free DED treatment technology, EyeSol® overcomes the traditional limitations of water-based formulations. EyeSol® is a novel odourless and colourless liquid with low surface tension and the same refractive index as water. Due to its unique physicochemical properties, EyeSol® spreads immediately over the ocular surface after instillation. Treatments use a small drop size of 10 µL that does not overfill the eye or initiate a blink reflex, which are common issues with water-based eyedrops. Due to EyeSol's water-free nature, EyeSol® products are preservative-free and surfactant-free, which is believed to greatly improve their tolerability compared with water-based drugs. The technology has been proven to be safe and well accepted, with one product already on the market in Europe and Australia.

Novaliq's late-staged products and pipeline in DED have the potential to break the vicious circle and redefine how DED is treated.

> "Recently, data has emerged from two clinical trials of novel topical drugs utilising a non-aqueous, preservative-free technology that may offer new and promising treatment approaches to improve the quality of life for DED patients in both segments of the disease."

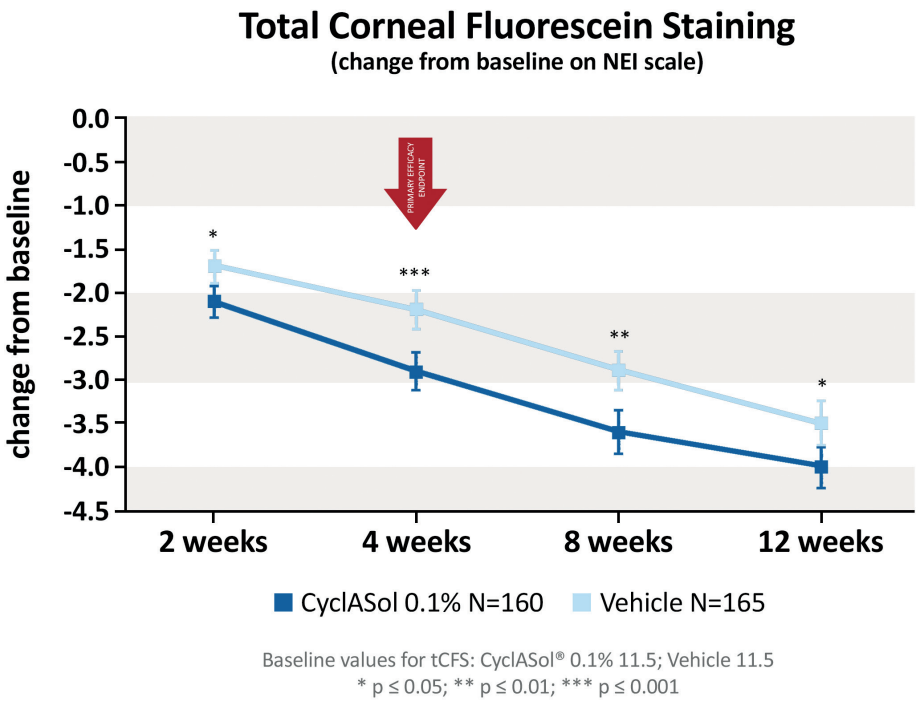


Figure 3: Primary efficacy endpoint of CyclASol® "ESSENCE" trial.

## CYCLASOL® – AQUEOUS-DEFICIENT DED

CyclASol® 0.1% is a clear ophthalmic solution of 0.1% cyclosporine A, an anti-inflammatory and immunomodulating compound, developed in EyeSol® for the treatment of predominantly aqueous-deficient DED. Advantages over other cyclosporine-containing ophthalmic treatments are CyclASol's improved efficacy and a fast onset of effect, combined with an excellent tolerability profile. The ESSENCE Phase IIb/III clinical trial, which comprised 328 patients across nine clinical sites in the US, was designed to confirm the results of the CYS-002 proof-of-concept trial, in which CyclASol® demonstrated beneficial effects versus its vehicle and the active control, Allergan's Restasis™, with excellent safety and tolerability.[14]

ESSENCE evaluated the efficacy, safety and tolerability of topical CyclASol® 0.1% for the treatment of patients with aqueous-deficient DED, with its primary efficacy endpoint at four weeks and continued dosing for efficacy and safety evaluations over a period of three months (Figure 3).

The ESSENCE trial met its primary efficacy endpoint, improvement of total corneal fluorescein staining over vehicle at four weeks, with high statistical significance ($p = 0.0002$). The effect began as early as two weeks after start of treatment and was maintained for the full duration of the study. Consistent with the previous clinical study, the central area of the cornea benefitted most. The clinical significance of these outcomes is further shown by a high responder rate (>50%) on both corneal (at four weeks) and conjunctival (at three months) staining.

The second primary endpoint Ocular Surface Disease Index® (OSDI®) assessment indicated that all patients benefitted from the treatment. Secondary endpoints on DED symptoms, as measured by the visual analogue scale (VAS), reached statistical significance over vehicle at four weeks. The study further confirmed the excellent safety and tolerability profile of CyclASol®. Adverse events occurred as a reaction at the treatment instillation site in 2.5% of the CyclASol®-treated group.

Novaliq believes that CyclASol® 0.1% unfolds the full potential of cyclosporine A for the first time in the treatment of DED and demonstrates the superior benefits of its non-aqueous, preservative-free, multidose formulation, allowing clinicians to treat more of their patients suffering from predominantly aqueous-deficient DED.[15]

## NOV03 – EVAPORATIVE DED ASSOCIATED WITH MGD

NOV03 (100% 1-perfluorohexyloctane) is a preservative-free, multidose ophthalmic solution and the first drug developed to treat evaporative DED associated with MGD. NOV03 uniquely treats DED associated with MGD based on a novel mode of action that balances the tear condition. Due to its low surface tension, NOV03 rapidly spreads across the ocular surface forming a layer at the tear film-air interface that prevents evaporation of the aqueous phase. Furthermore, it has the ability to penetrate meibomian glands and potentially dissolve thickened meibum, thereby improving meibomian gland function.

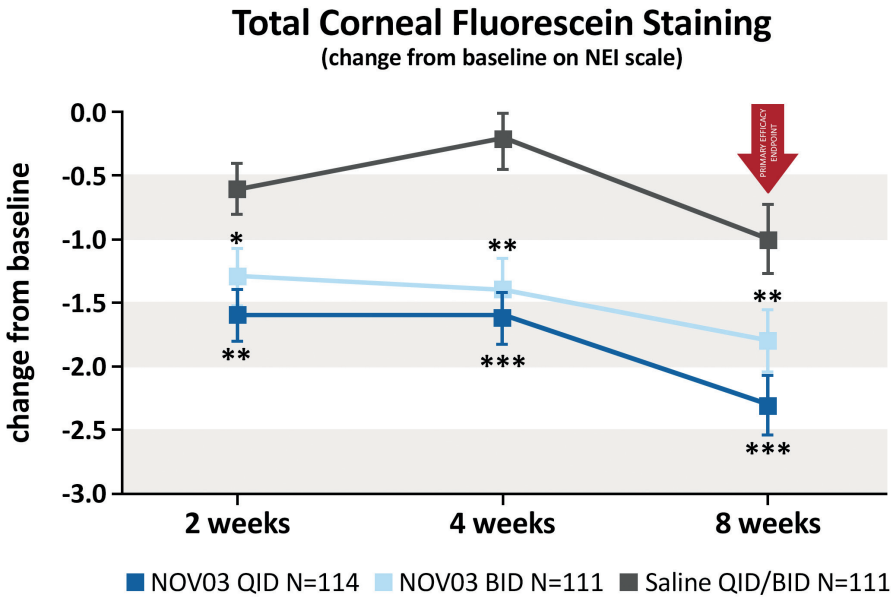


Figure 4: Primary efficacy endpoint of NOV03 in "SEECASE" trial.

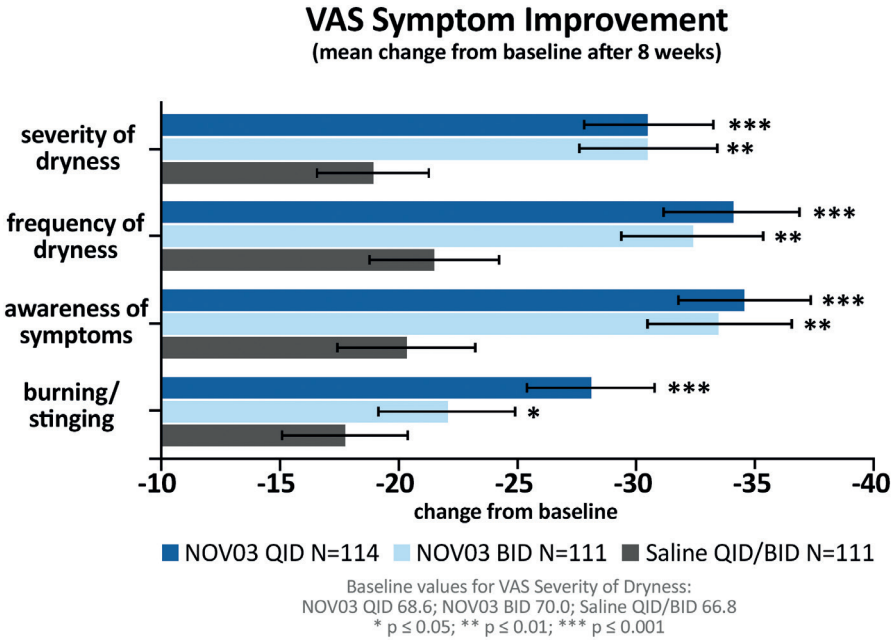


Figure 5: Symptom improvement by NOV03 in "SEECASE" trial.

Novaliq conducted the SEECASE Phase II clinical trial, which comprised 336 patients across 10 clinical sites in the US. SEECASE was a multicentre, randomised, double-masked, saline-controlled clinical trial. The trial was designed to evaluate the effects of NOV03 according to two different dosing regimens on signs and symptoms of DED. SEECASE evaluated its primary efficacy at eight weeks.

The SEECASE trial met its pre-specified primary endpoint, improvement of total corneal fluorescein staining over control at eight weeks, with high statistical significance for both dosing regimens, four times daily (qid) and twice daily (bid) ($p<0.001$ and $p=0.009$, respectively) (Figure 4). The effect started as early as two weeks after start of treatment and was maintained over the full duration of the trial for both treatment regimens. In addition, NOV03 showed pronounced, statistically significant improvement in various symptoms over control (Figure 5). In particular, the magnitude of effect on symptoms was impressive: patients reported on average a 40–50% improvement over their baseline depending on the parameter examined at eight weeks. Thus, this first-in-class treatment shows great promise for patients with evaporative DED associated with MGD.[15]

For both drugs, final clinical trials will start in 2019, leading to NDA filings in 2021.

## CONCLUSION

DED is a chronic, multifactorial disease that impacts the functional vision and quality of life of patients. Due to different underlying root causes and pathogeneses, targeted therapies for the different disease segments are required to improve patient outcomes.

- Predominantly evaporative DED associated with MGD is regarded as the primary cause of DED, but therapeutic options for its treatment are limited. NOV03 is a promising treatment option specifically targeting and treating this form of DED.
- CyclASol® addresses predominately aqueous-deficient DED for patients requiring an anti-inflammatory treatment.

Targeted treatment options like CyclASol® and NOV03 based on a non-aqueous, preservative-free technology give hope that new drugs can help provide more patients with a satisfying treatment solution, improving and preserving their vision and quality of life.

## ABOUT THE COMPANY

Novaliq is a pharmaceutical company focusing on the development and commercialisation of first- and best-in-class ocular therapeutics based on EyeSol®, the world's first water-free technology for ophthalmology products. With an initial focus on dry eye disease (DED), Novaliq offers an industry-leading portfolio addressing the unmet medical needs of millions of patients with DED. Novaliq's lead assets in late-stage clinical development are:

- CyclASol®, an anti-inflammatory and immunomodulating drug for the treatment of DED with a demonstrated early onset of action and excellent tolerability.
- NOV03, the first drug addressing evaporative DED associated with meibomian gland dysfunction (MGD).

NovaTears® water-free eyedrops for DED are CE marked and are commercialised in Australia/New Zealand by AFT Pharmaceuticals and in Europe as EvoTears® by Ursapharm.

Novaliq is headquartered in Heidelberg, Germany and has an office in Cambridge, MA, US. The long-term shareholder is dievini Hopp BioTech Holding (Walldorf, Germany), an active investor in life and health sciences companies.

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## ABOUT THE AUTHOR


**Christian Roesky** is Chief Executive Officer of Novaliq. He holds a PhD in chemistry and has been involved in eyecare for more than 15 years. Dr Roesky has extensive operational experience at multiple international pharmaceutical companies, having worked in the US, Spain and Switzerland. He has served as General Manager for Bausch + Lomb GmbH; as Commercial Director, Central Europe of Abbott's Diagnostics Division; as General Manager and Speaker of the German Country Management Board of Abbott in Wiesbaden; and as General Manager of Alcon Germany & Austria (Novartis).

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# INTRAVITREAL INJECTION OF VEGF INHIBITORS – IMPACT OF DRUG CONTAINERS

Against a background of increasing use of intravitreal injections of vascular endothelial growth factor inhibitors in the treatment of numerous serious ocular diseases, Douglas Cusato, Director of Medical Rubber Business, Sumitomo Rubber, North America, provides a detailed comparative analysis of the regulatory requirements, patient risks, costs, benefits and other considerations when using either products supplied from pharma manufacturers in a prefilled syringe format, or from compounding pharmacies, which fill the formulation into general-use or insulin syringes.

## BACKGROUND

Since the early 2000s, intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors have become the treatment of choice for various eyesight-threatening eye diseases including macular degeneration (MD), diabetic retinopathy (DR), retinal vein occlusions (RVO) and retinopathy of prematurity (ROP).[1] Two common sourcing practices for clinics and hospitals include obtaining Avastin (bevacizumab) injections from compounding pharmacies in various syringe packaging configurations, or Lucentis (ranibizumab) in a traditional prefilled syringe (PFS) format.[2] A breakdown of the packaging configurations and materials of construction can be found in Table 1.[3-5]

Of course, there are various advantages and disadvantages linked with each configuration, including aseptic assurance, preparation steps, administration time, packaging system intended use and overall cost of the packaged drug product.

Essentially, the main driver for clinics and hospitals to use compounded Avastin in plastic general-use and insulin syringes is overall cost. A compounded Avastin injection costs an average of US$50-60 (£39-47) versus $1500 per dose for Lucentis.[6] This has a significant impact on much of the healthcare system including health insurance reimbursements, patient out-of-pocket costs and overall financial liabilities for the clinics and hospitals.[6] Additionally, considering there are numerous publications referencing the clinical performance of the two options and their comparability, it's reasonable to understand why this is a common practice.[7-8] In short, some view it as a safe, effective and cheaper option.

## INDUSTRY CHALLENGE

From 2006 onwards, numerous reports started to be published describing adverse events linked with compounded drugs for intravitreal injection such as Avastin including increase in intraocular pressure (IOP), infections and "floaters".[9-14] Floaters can be described as small particles that are visible to the patient following intravitreal injections and various reports conclude these are linked with silicone oil microdroplets. Due to the growing concerns, there has been an increase in regulatory security related to repackaging such drug products and additional supply restrictions have been imposed to minimise such practices in the future.[15-16]

With regards to publications, reports related to clinical outcomes demonstrate similar performance between both compounded Avastin and the traditional PFS Lucentis product. However, the outputs from product quality investigations are quite conflicting. Various reports observe favourable comparability, but others demonstrate significant variation between sources of compounded Avastin and the originally packaged vial product.[17-20]

From a high-level view, the syringe selection used by compounding pharmacies to repackage Avastin makes a lot of sense. The selected formats enable fewer preparation steps via providing a PFS concept, lower overall product cost and access to pre-assembled syringes with some of the smallest gauge needles on the market. However, from a factual point of view, utilising plastic general-use and insulin syringes as a storage and drug delivery device for intravitreal injections comes with numerous challenges and risks. Most of the concerns stem from the fact that these syringes were designed to support an

**Douglas Cusato**
Director of Medical Rubber Business
T: +1 909 694 3178
E: DCusato@srnatire.com

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| Syringe | Filling Source | Typical Syringe Materials of Construction |
|---|---|---|
| Plastic General Use Syringe  | Compounding Pharmacy | • Luer cone configuration<br>• Polypropylene or polycarbonate syringe barrel (USP Class VI plastic)<br>• Barrel silicone lubricant (medical grade from Dow Corning)<br>• Polypropylene tip cap (drug contact)<br>• Rubber plunger (polyisoprene, styrene butadiene rubber, butyl rubber and thermoplastic elastomer)<br>• Plunger stopper lubricant (medical grade from Dow Corning) |
| Plastic Insulin Syringe  | Compounding Pharmacy | • Staked needle configuration<br>• Polypropylene or polycarbonate syringe barrel (USP Class VI plastic)<br>• Barrel silicone lubricant (medical grade from Dow Corning)<br>• Polypropylene needle cover (non-drug contact)<br>• Adhesive to hold cannula / needle in barrel<br>• Rubber plunger (polyisoprene, styrene butadiene rubber, butyl rubber and thermoplastic elastomer)<br>• Plunger stopper lubricant (medical grade from Dow Corning) |
| Glass Prefilled Syringe  | Pharma Company and/or CMO | • Glass syringe barrel (Type 1 glass)<br>• Barrel silicone lubricant (medical grade from Dow Corning or baked-on silicone oil)<br>• Rubber tip cap (bromobutyl rubber material (drug contact) with plastic rigid cover)<br>• Rubber plunger (bromobutyl rubber material with fluoropolymer coating)<br>• Plunger lubricant (medical grade from Dow Corning) |

Table 1: Comparison of typical syringe packaging linked with intravitreal injections of anti-VEGF drugs.

entirely different use. More specifically, the larger challenges and risks include:

- Overall product requirements and product performance
- Supply chain management and change controls
- Fill-finish for insulin syringes and needle quality.

## Design Requirements and Technical Specifications

Within the US, general-use and insulin syringes are filed and approved as medical devices. As such these devices receive approval via the FDA's 510k process and are developed under the construct of various inputs including but not limited to 21 CFR 820 and Design Control Guidance for Medical Device Manufacturers. From the Design Input section of the Quality System Regulation (21 CFR 820.30(c)), the FDA has listed this view point: "Each manufacturer shall establish and maintain procedures to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient."[21]

The output of the design requirements feed the technical specifications for the final device.[3-5] Although the technical specifications are certainly extensive and have proved favourable to support general use and insulin syringes from development through decades of commercial use, there are several areas of concern that would typically be linked with PFS delivery systems for intravitreal injections that are not necessarily covered in the specifications for general-use and insulin syringes. These include:

- USP 789 compliance – Particulate for intravitreal injections
- USP 1207 alignment – Container closure integrity
- ISO 11040 compliance - Prefilled syringes
- ISO 11608 compliance – Needle based injection systems for medical use
- Drug potency following syringe storage
- Syringe functional performance following storage.

A degree of reassurance is provided by Appendix A of the FDA's Industry Guidance, "Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application", covers various components including:[22]

- Subvisible particulates
- Protein content
- Potency
- Product related impurities
- Sterility test at the time that its repackaged
- Sterility or container closure integrity (CCI) testing after ageing.

Although the FDA guidance mentioned above certainly promotes a reduction in risks related to use of compounded syringe products for intravitreal injections, there are additional factors to consider. For example, during a recent anonymous survey related to PFS / primary container design and development, 30 industry engineers from the various leading pharmaceutical companies, PFS manufactures, and well-known design consultant agencies shed some light on some of the common challenges they had experienced. The results of this study can be found in Figure 1.

Along with providing insight into the challenges linked with developing such devices, this data also provides useful feedback related to overall patient risks. Although challenges related to particulates, extractables and leachables, chemical compatibility and CCI of nominally designed syringe devices are well acknowledged, the most common development challenges are linked with overall product design, design robustness and impact of process capabilities / control plans. This is particularly interesting if you consider a gap analysis between the survey results and the contents in Appendix A of the FDA's Industry Guidance, "Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application", versus the green highlighted section in the Figure 1 survey results graph.

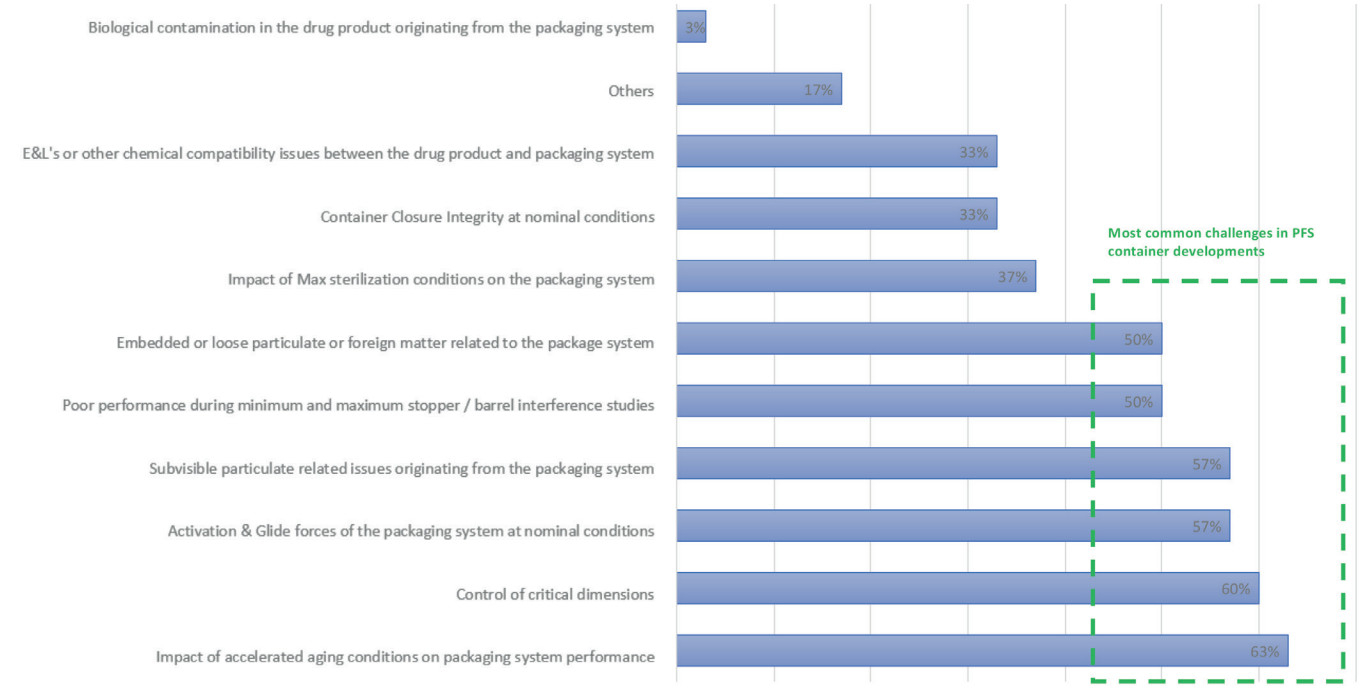


Figure 1: Survey results from 23 industry PFS R&D engineers

## Supply Chain and Change Control

Another notable challenge is the drastic difference in supply chain management. Common practice for compounding pharmacies is to source sterile syringes from medical equipment distribution organisations. Such a supply chain inherently creates a more distant relationship between the owner of the final packaged drug product (e.g. compound pharmacy) and the design owner of the sterilised empty container (device supplier). This situation is completely different from the typical relationship within the traditional PFS industry, where device vendors and pharmaceutical companies essentially partner during most phases of the development process and continuously have transparent communications to ensure the product being manufactured is well characterised and the relationship between the device and the drug product are clearly understood. This also continues throughout the lifecycle of the drug.

Change control processes represent a critical aspect of supply chain management. In the traditional PFS space, pharmaceutical companies are given access to a host of technical and proprietary information related to material and manufacturing processes under confidentiality agreements. Not only are these details directly linked with buy specifications and supply agreements, they are also included within drug master files (DMFs). The DMF allows for the FDA to sanity-check technical inputs related to the packaging supplier and components and cross-check them against the final packaged drug product description, labelling, etc. All this effort provides the foundation for a robust supply chain, that is well structured to manage the unavoidable changes that occur during lifecycle of a drug product.

Although not specifically related to intravitreal injection, a nonetheless relevant example of the challenges that can be created with the compound pharmacy supply chain model for syringes occurred in 2015. In the summer of 2015, the FDA published multiple warning letters that specifically identified risks linked with compounded or repackaged drug products in general-use syringes that were being utilised as both a drug storage and delivery device. Overall, this included a considerable number of different sized general-use syringes (1, 10, 20 and 30 mL) and the focus was mostly on various products on the FDA drug shortage list including fentanyl, rocuronium, neostigmine, morphine, midazolam, methadone, atropine, hydromorphone, cisatracurium and remifentanil.[23] According to reports related to this circumstance, risk of potency loss was linked with any syringe stored for more than 24hrs,[24] which is a far shorter duration than some compounded drug products experience in syringes.

In the abovementioned potency loss situation, an alternative plunger stopper supplier that was utilised within the popular syringe product line was identified as the root cause. The FDA later announced that the syringe supplier had completely converted all syringes back to the original stopper supplier.[23]

With a traditional PFS drug product, such a scenario should be impossible as the primary packaging components are approved by regulatory bodies as essentially a constituent of the drug product and are very much treated with the same level of scrutiny as, for example, excipients within the formulation. Any significant modification of the manufacturing process or change to the raw materials utilised to produce these packaging components is considered a significant change. When a component does need to be changed, a situation that certainly arises within industry, pharmaceutical companies steer towards the conservative side and implement formal change control processes including new drug compatibility, extractables and leachables and toxicology assessments, product functional studies and ageing studies, to ensure the change in the device still supports a safe and effective product for the end patients.

## Needle-Point Concerns

Lastly, an additional set of concerns that are specifically linked with compounded drug products for intravitreal injections that are repackaged in insulin syringes includes:

- Needle-point quality following fill via transfer from a Luer lock syringe
- Needle-point quality following re-assembly of the rigid plastic needleshield
- Needle-point contamination during re-assembly of the rigid plastic needleshield

During the compounding process with insulin syringes, various techniques are utilised including withdrawing the drug product from the originally packaged vial. Some pharmacies use a technique in which multiple doses are withdrawn from the vial using a general use Luer lock syringe, followed by the insulin syringe needles being inserted into the Luer cone and a final dosage being drawn up within the insulin syringe.[25] With regards to the second concept, insulin syringes are clearly not designed to be insert into a Luer cone. Even highly skilled operators could struggle with such a manual process and thus repeatability is a major concern. If the needle is damaged via colliding with the Luer cone during this process and not detected prior to use, patients could experience a significant increase in pain perception or even more extensive damage to the eye itself.

Following either of the filing techniques for insulin syringes mentioned above, the protective rigid needleshield is reassembled over the needle and onto the syringe hub. With regards to the manual re-assembly process, the main challenge experienced by common syringe users (e.g. insulin dependent diabetics, nurses, doctors, etc.) is that continuously aligning the cap over the syringe needle takes a set of steady hands, good visibility and high level of attention. This could have significant risks linked with transfer of bloodborne pathogens. The other concern is that if the plastic cap collides with the needle tip, it could damage the point. Again, if not detected prior to use, the results could be similar to those mentioned for the needle colliding with the Luer cone – pain or damage to the eye.

## POTENTIAL SOLUTIONS AND MOVING FORWARD

It is clear that compounded VEGF inhibitors for intravitreal injections will continue to have a future within industry; they have several advantages. Thus, the question is, what development concepts, technologies, products and processes can support such a concept in the future to improve patient safety and reduce risk, mitigating the concerns detailed here? This is a broad question with numerous inputs and potentials and warrants continued discussion. Potential areas to explore for improvement include:

- Development structure of compounded products in storage / drug delivery devices
- Supplier relationship between device suppliers and compound pharmacies
- Advanced syringe components / syringe system technologies
- Syringe fill-finish technologies.

### Development Structure

With regards to development structure, it clearly makes sense to treat compounded products in any syringe that is both a storage and drug delivery device as a traditional PFS. As such, there are various things to consider including development team structures and expertise and design controls. PFS development project teams are normally composed of leading experts in product design, statistics, usability, regulatory, design control and manufacturing technology. Such skilled individuals working towards a common goal leads to a robust product, built on a solid foundation of data that focuses on critical regulatory inputs and most importantly the needs of the user and patient. It is quite feasible that these skill sets could create a significant financial burden for the smaller compounding pharmacy to absorb. Thus, another option is for such organisations to outsource this to device development firms or the suppliers of the devices.

Some of the advantages to leveraging the expertise of the supplier is that compound pharmacies will create an improved supplier relationship and gain accessibility to components and tools to support a more robust development. For example, suppliers can provide min/max challenge devices (size, sterilisation, silicone, etc) to support product characterisation and ensure a clearly defined design space is realised.

PFS development projects are commonly resourced to support the evaluation of tens-of-thousands of assembled devices with quality requirements that are linked with ppm-level defect rates in order to demonstrate appropriate process controls. This is clearly an area for improvement with regards to compounded syringes, as today it is far more common that all testing takes place using a limited sample of commercial production products. Such practices don't necessarily capture batch-to-batch variation.

Also related to the actual development process, it has become an industry standard and required by CFR 820 for organisations to host formal design reviews for drug delivery device development efforts. Such reviews intentionally include leading experts that thoroughly review design inputs, product requirements and supporting data, to ensure the PFS / drug delivery device product is a robust and safe solution for end users and patients.

Within CFR 820, the following can be referenced regarding design reviews: "Each manufacturer shall establish and maintain procedures to ensure that formal documented reviews of the design results are planned and conducted at appropriate stages of the device's design development. The procedures shall ensure that participants at each design review include representatives of all functions concerned with the design stage being reviewed and an individual(s) who does not have direct responsibility for the design stage being reviewed, as well as any specialists needed. The results of a design review, including identification of the design, the date, and the individual(s) performing the review, shall be documented in the design history file (DHF)".[21] It seems practical to assume resources from device companies or external consultant firms could support such design reviews as a subject matter expert. By hosting such reviews, compound pharmacy organisations would ensure they have formal industry expertise reviewing the product for overall robustness and safety.

### Supplier Relationship Management

Supplier management relationship efforts can support improved product quality and end-user risk reduction related to compounded products in syringes via multiple mechanisms. As mentioned above, change control agreements could be integrated to support the specific needs of compound pharmacies. Of course, this concept will cost more time and resources and ultimately will create discussions related to overall product sales price. However, such concepts are supported by phrases such as "total cost of ownership". Within such models, paying more for a robust drug delivery system, certainly outweighs the impact linked with a major market recall or, even worse, injury to end users. Additionally, documentation utilised by the PFS industry including, for example, technical files and DMFs, could be referenced by compound pharmacies to ensure the container systems are well defined. This would inherently limit the potential for changes to be made to the container system without prior notification.

### Advanced Components / Syringe Technologies

Advanced rubber plungers for syringe systems, fully or partially coated with fluropolymer film, are generally linked

with low extractable and leachable rubber materials. The coating material is applied to at least the drug contact area of the rubber stopper surface. The halobutyl base-rubber formulations used are already low in extractables and leachables and composed of inert materials, especially compared with the more conventional / legacy polyisoprene or SBR formulations. Along with the base polymer being composed of a more inert polymer material, premium rubber components use far less ingredients then legacy materials. An example of a premium rubber formulation can be found in Table 2.[26]

Most of leading vendors within industry have such offerings within their product portfolio but it's not common practice for these to be utilised within general-use plastic syringe systems, which tend to use conventional / legacy materials.

The coating of advanced plungers provides an additional source of risk reduction for improved patient safety and overall improved drug product quality via better drug compatibility, reduction in extractables and leachables.

Advanced plungers can also enable silicone-free primary packaging, contributing directly to a reduction in silicone-related subvisible particles (SbVPs). Silicone-related SbVPs have been identified as a source of "floaters" experienced by ophthalmic patients following intravitreal injection. Additionally, the overall design of premium-coated stoppers supports a reduction in activation and glide forces (AGF) compared with legacy components. Figure 2 shows examples of commercially available partially and fully coated stoppers.

Next-generation siliconised syringe options are offered by multiple vendors. They offer a variety of sizes and configurations including both Luer lock and staked-needle designs. These syringes are offered in plastic and glass materials and the siliconisation technologies utilised during the manufacturing of these products supports reduction of risk related to silicone SbVPs.

| Premium Rubber Component Composition | | |
|---|---|---|
| Ingredient | phr | Description |
| Brominated isobutylene-co-para-methylstyrene | 100 | Elastomer |
| Polestar 200R | 90 | Filler |
| Parapol 2255 plasticiser | 5 | Plasticiser |
| Polyethylene wax | 3 | Processing aid |
| TiO2 | 4 | Colourant |
| MgO | 1 | Curing agent |
| Diak 1 vulcanising agent | 0.75 | Curing agent |

Table 2: Premium rubber composition.

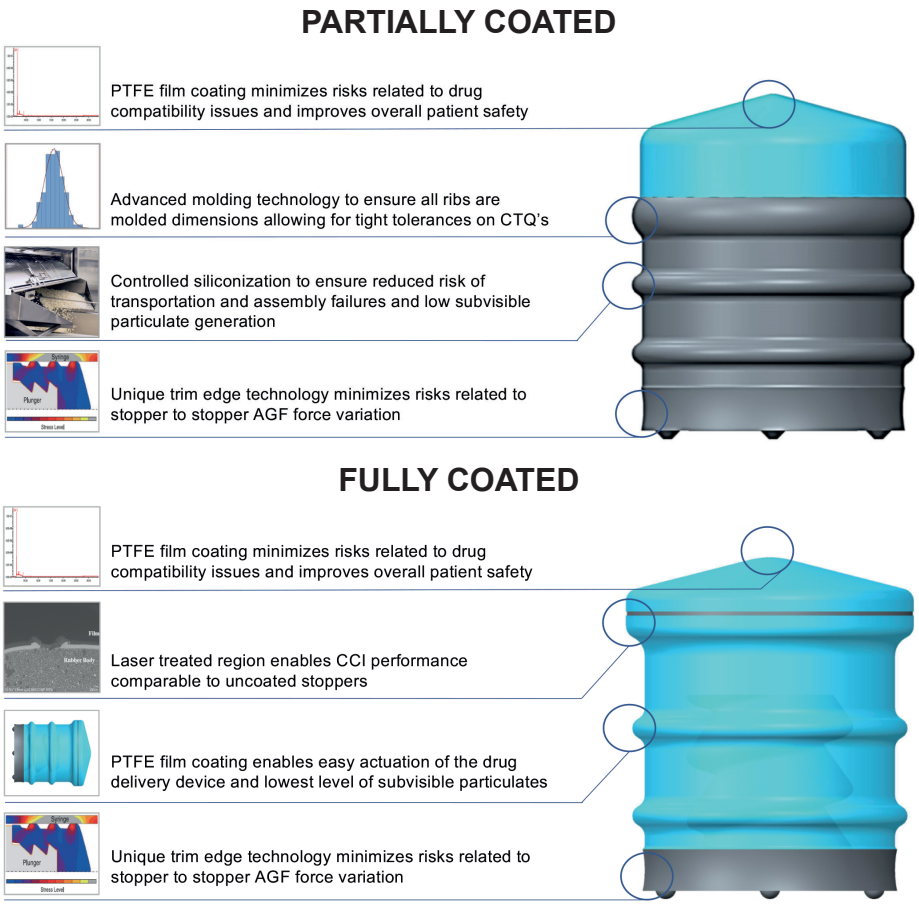


Figure 2: Partially coated and fully coated plungers.

Based simply upon surface area, siliconisation in the syringe barrel has a far greater impact on silicone-related SBvPs particulates compared with rubber. However, both provide opportunities for risk reduction. For siliconised syringes, the silicone is a critical feature of the syringe and supports the assembly of the stopper into the barrel after filling and the actuation forces of the syringe, although other syringe features also play a role such as inner diameter of the needle itself and viscosity of the drug product.

A selection of example advanced PFS systems are described in Box 1.

One challenge linked with most of the innovative technologies mentioned in Box 1 that significantly limits their use in compounding pharmacy setting includes the syringe products' final configuration and packaging. Unlike general-use and insulin syringes, the technologies mentioned above are delivered with the stopper and plunger unassembled from the syringe barrel. Thus not only is filling required but assembly is required as well. Unfortunately, without proper fill-finish equipment, safe and effective filling and assembly of such syringe would be extremely challenging. An advantage to using the nested syringes is that they are not filled via the needle end of the syringe. This avoids the need to manipulate or reassemble the syringe during the filling process, and inherently reduces risks linked with reassembly of the rigid cap onto the syringe.

As final packaging linked with all the technologies on Box 1 are configured

## BOX 1: ADVANCED PFS SYSTEMS: OVERVIEW AND EXAMPLES

Becton Dickinson launched a premium quality syringe called Neopak™ XSi™.[27] According to publicly available information on BD's website, Neopak XSi provides overall improved product quality and a significant reduction in silicone-related SBvPs compared with traditional siliconised PFS; >95% in one published study, which also reported that XSi does not sacrifice actuation performance.[28]

Gerresheimer offers siliconised glass syringes with a baked-on silicone technology called Gx® Baked-on RTF® glass syringes. The company's published information states that the product is patented in Europe and the US for the packaging of sensitive biotechnological medications that may interact with free silicone oil droplets. The intent of this product is to reduce the number of free silicone oil droplets significantly. As well as enabling a reduction in silicone related subvisible particulates, the Gx® Baked-on RTF® technology offers reliable hydrophobic properties and especially low breakloose and gliding forces that remain stable throughout the storage period.[29]

The TopPac® line from Schott is one of the most successful plastic PFS offerings on the market today. According to public company information, the TopPac cyclic-olefin copolymer (COC) syringe product is injection moulded, which enables significantly improved dimensional tolerances over glass. The tighter dimensional tolerances along with Schott's crosslinked siliconisation process provide consistent glide forces, resulting in precise and smooth drug delivery. The crosslinked siliconisation process is applied after the moulding step and cooling phase. A reactive silicone is applied to the internal surface of the syringe system followed by a curing process. The process is designed to ensure consistent distribution of silicone throughout the syringe barrel along with extremely low levels of free silicone oil.[30]

Silicone-free syringes have also been under development throughout industry for many years and various products have launched across the world. In reality, there continues to be some market concern related to product functionality such as actuation forces and container closure integrity.[32] However, improvements have been made. For example, Terumo launched the PLAJEX™ plastic silicone-free syringe system that utilises an inert cyclic-olefin polymer (COP) and high-quality rubber stopper with a proprietary coating. Based upon a technical report published by Terumo, the PLAJEX™ product line demonstrated a SBvP count of 2/mL versus 900/mL for a traditional siliconised syringe.[33] Earlier this year Terumo announced that this syringe system had been qualified with a manufacturer of a biosimilar version of Humira (adalimumab) and had received European regulatory approval.[34]

to support fill-finish operations such as Isolator technologies, a barrier limiting their usage by compounding pharmacies is proper fill-finish equipment. Historically, such fill-finish equipment has been designed for volumes in the billions of units.[35] Additionally, as mentioned in the previous section, compounders have become very comfortable with manual operations under a hood with laminar flow.

However, in recent years, several leading fill-finish suppliers have begun to develop and launch unique modular technologies that are suitable for clinical- and small production-volume filling. Additionally, most of this equipment is being designed to support the filing of multiple packaging configurations via the modular unit concept and simple change parts. This provides a means for compounding pharmacies to leverage the efficiencies compared with manual filing, and ultimately support return on investment in the cost of the sophisticated fill-finish equipment.

During an interview at INTERPHEX 2016, Bausch + Stroebel representatives explained the value of the company's flexible modular VarioSys® equipment, highlighting continuing opportunities of these machines for compounding pharmacies undertaking with small-batch filling, quick changeovers and a diverse portfolio of container closure system designs including nested vials, PFS and cartridges, for example.

Various organisations are working to support compounding pharmacies with proper fill-finish equipment, for example, AST Technologies with their GENiSYS® c20 isolator, and Colanar Inc.

During a recent discussion, Colanar President Bernd Stroeter explained that "503B compounding pharmacies have been converting from manual vial filling operations to benchtop vial filling machines in recent years. These benchtop filling machines are particularly suited as the first automated filling equipment due to a number of advantages, from their compact design and high build quality to their reasonable cost and ease of use. Further advantages are their flexibility to process vials, PFS and cartridges on the same machine, and their ability to be used in laminar flow workbenches, RABS enclosures, and isolators. Since the pharma industry is rapidly moving towards isolator technology, compounding pharmacies will also have to adopt this technology and acquire additional technical know-how in order to be able to operate this increasingly complex equipment".

Colanar has supplied various benchtop vial filling systems that can be incorporated into hoods with laminar follow, which seems to be the comfort zone for many organisations. Additionally, there is growing interest for further vial filling machines, and companies like Colonar Inc are now starting to get requests for syringe filling machines. Illustrations of Colonar's various platforms to support compounding vial and syringe fill-finish operations can be found in Figure 3.

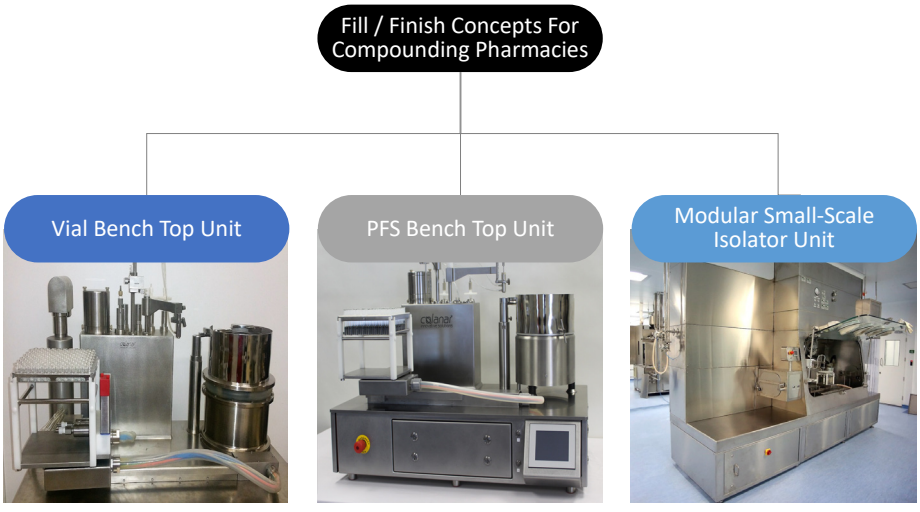


Figure 3: Colanar's modular vial, PFS, cartridge fill-finish equipment. (Images provided by Colanar, Inc.)

## CONCLUSION

Overall, intravitreal injections of VEGF inhibitors continue to be a growing trend within industry. As regulatory guidance continue to provide clarity and compounders capture the value from premium packaging systems, the robustness and safety of the compounded products will continue to improve.

In the meantime, it is critical that industry communicates on the challenges and ideally establishes best practices regarding fill-finish process and equipment, packaging system selections, and testing structures, to ensure proper syringe system functionality and overall compounded product safety.

It also makes sense for compounders and device suppliers to improve partnerships, as pharma and PFS device suppliers have done with considerable effectiveness. Compounders will continue to fill and sell compounded drug products in general-use and insulin syringes, so a transparent relationship is needed to ensure the safety of the device is was established and maintained throughout the lifecycle of the commercial relationship. All this certainly requires time, resources, effort and, more than likely, investment too, but the level of risk reduction that these practices bring to the overall situation is priceless.

## ABOUT THE COMPANY

Since its founding in 1909 as the first modern rubber factory in Japan, Sumitomo Rubber Industries has strived to produce advanced, environmentally friendly products based on the latest innovations in rubber technology. The medical rubber group is focused on providing the highest quality products and ultimately dedicated to improving the lives of people around the world. Utilising the latest in material and process innovations and a global manufacturing footprint, Sumitomo Rubber Industries delivers consistent high-performing products and provides strong assurance of supply.

## REFERENCES

Reference list available online at www.ondrugdelivery.com.

## ABOUT THE AUTHOR

**Douglas Cusato** is Director of the Medical Rubber Business for Sumitomo Rubber, North America. In this regional leadership role, he is responsible for all aspects of the North American business including strategy, R&D, operations and sales. Mr Cusato has been active in the parenteral packaging industry since 2006 and has served in various technical leadership roles with a focus on technology and platform development. He has chaired multiple industry taskforces and participates in numerous groups as a subject matter expert in elastomeric components for parenteral packaging applications. Mr Cusato holds a Bachelors' degree in Chemistry from Rutgers University (NJ, US).

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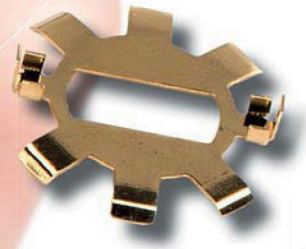

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# ACCURATE, PRECISE MICROLITRE DOSING WITH PREFILLABLE SYRINGES FOR OPHTHALMIC INJECTIONS

In this article, Gautam Shetty, PhD, Chief Executive Officer, Congruence Medical Solutions, discusses the challenges inherent to delivering microlitre dosage volumes accurately from a standard prefilled syringe, and introduces Congruence's Microlitre Dosing Syringe (MDS) platform as a solution.

## INTRODUCTION

In the US, there are now more procedures involving ophthalmic injections than cataract surgeries performed annually. This is primarily driven by the advent of drugs that target vascular endothelial growth factor (VEGF) in the treatment of diseases such as:

- Age-related Macular Degeneration (AMD)
- Diabetic macular oedema (DME)
- Diabetic retinopathy (DR)
- Retinal vein occlusions
- Retinopathy of prematurity (ROP).

Other drugs are also used for treatment of eye infections (and the resulting endophthalmitis), uveitis and post-cataract prophylaxis. It is estimated that, in 2016, six million intravitreal injections were administered in the US alone. With an ageing population and increasing incidence of diabetes, the number of such injections is expected to continue to rise.

Currently, there are two commonly used, approved anti-VEGF agents – Eylea®, marketed by Regeneron Pharmaceuticals (Tarrytown, NY, US) in the US, Bayer (Leverkusen, Germany) in Europe and Santen (Osaka, Japan) in Japan; and Lucentis®, marketed by Genentech (San Francisco, CA, US) in the US and Novartis (Basel, Switzerland) outside it. Eylea® and Lucentis® represented 26.3% of all Medicare Part B spending in 2016.[1] Despite their relatively small unit volumes, these high-value drugs represent an important part of the healthcare system and have

> "The typical dose volume for ophthalmic injections is 50 uL, but delivering such a small dose volume with a conventional hypodermic syringe or PFS is challenging.."

| | 0.5 mL PFS | 1 mL Long PFS |
|---|---|---|
| Syringe Diameter (mm) | 4.65 | 6.45 |
| Dose Stroke Sensitivity (µL/mm) | 17.0 | 32.7 |

Table 1: Injection dose stroke sensitivity.

**Dr Gautam N Shetty**
Chief Executive Officer
T: +1 216 272 5521
E: GS@CongruenceMed.com

**Congruence Medical Solutions, LLC**
3000 Falls Road, Suite 200A
Baltimore
MD 21211
United States

**www.microliterdose.com**

drawn biosimilar interest. In addition to the anticipated biosimilar activity in this space, there are a number of novel drugs in the clinical development pipeline.

## PREFILLED SYRINGES FOR OPHTHALMIC INJECTIONS

There are numerous benefits to using a prefilled syringe (PFS) for ophthalmic injections. The benefits of using a PFS include:

- Lower incidence of exogenous endophthalmitis arising from infection in the eye. Endophthalmitis is considered one of the most serious adverse events related to intravitreal injection, leading to blindness or even patient death. This lower occurrence rate may be attributed to there being fewer use-steps associated with a PFS.[2]
- Reduction in syringe preparation time of 27–39%, which could provide a substantive benefit to clinicians, considering the increasing trend in number of injections administered.[3]
- Mitigating reported risk from leachable-mediated intra-ocular inflammation, which is suspected to be associated with use of some hypodermic syringes. Presence of leachable silicone has resulted in several lawsuits (including class action) in the US, which could be addressed by employing either baked-on silicone or silicone-free PFS.[4,5]
- Reducing drug fill volume (compared with a vial), potentially increasing effective drug product yield for a given drug stock solution.
- Reducing downstream packaging costs associated with injection kits, thereby streamlining supply-chain operations.

Novartis launched the Lucentis® PFS in 2014 and Genentech launched its own in 2017. Regeneron Pharmaceuticals has indicated a launch of a PFS for Eylea® in 2019. For biosimilars and other novel drugs in the development pipeline, PFS for ophthalmic injections shouldn't be merely a consideration for product lifecycle management. Clinicians have indicated strong preference for prefilled delivery options.

> "The Congruence MDS platform consists of a dose-controlling plunger rod subassembly adapted to integrate with a standard 1 mL long PFS."

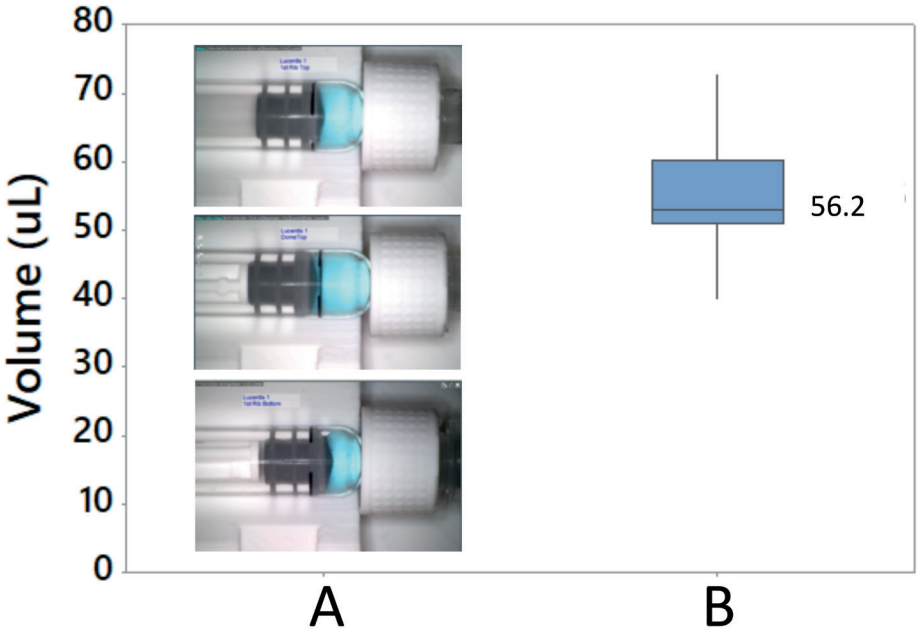


Figure 1: User data with 0.5 mL PFS for a 50 µL dose: sample images of variation in dose start position (A), and measured dose for 21 users (B).

## CHALLENGES TO ACHIEVING ACCURATE, PRECISE MICROLITRE DOSES

The typical dose volume for ophthalmic injections is 50 uL, but delivering such a small dose volume with a conventional hypodermic syringe or PFS is challenging.[6] The plunger travelling only a millimetre results in the dispensing of 17 µL and 32 µL, in 0.5 mL standard PFS and 1 mL long standard PFS, respectively (Table 1). Hence, any slight error or variation at start-of-dose or end-of-dose results in a disproportionate degree of inaccuracy. Setting a dose in a conventional system by aligning the plunger stopper with a marking on the syringe barrel tests the limits of human capability. Data from a user study involving retina specialists illustrates the limitation of a conventional PFS in this regard (Figure 1).

A syringe having an internal diameter smaller than that of a standard 0.5 mL PFS could potentially improve accuracy when delivering a microlitre sized dose. However, integration with standard pharmaceutical fill-finish infrastructure would be challenging with non-standard PFS systems. Any consideration for a non standard PFS would need significant capital investment in PFS component development and development of custom fill-finish equipment.

The same issue arises with the injection of a 50 µL dose using 1 $cm^3$ hypodermic syringes, which are of a similar internal diameter to 0.5 mL PFS. This is widely reported in the literature[7] and was highlighted in a presentation at the American Academy of Ophthalmology (AAO) meeting in Chicago, IL, US in October 2018. This inaccuracy and imprecision is reported not only between uses for the same user but also between users. It can be a significant issue for applications where the therapeutic window is extremely narrow, such as injections in pre-term neonates diagnosed with ROP. Additionally, accuracy and precision of the delivered dose are critical to the fidelity of clinical data used to measure drug effectiveness, for example in dose-ranging studies.

Chronic ocular diseases such as AMD and DME require regular intra-ocular injections, usually monthly. Frequent under-dosing could result in suboptimal clinical outcomes, whereas overdosing could result in complications, such as increased, sustained intra-ocular pressure (IOP) post-injection, requiring secondary interventions. It is therefore key to the treatment of such conditions to deliver the dose required accurately, every time.

## CONGRUENCE MICROLITRE DOSING SYRINGE DEVICE

The Congruence MDS device consists of a dose-controlling plunger rod subassembly adapted to integrate with a standard 1 mL

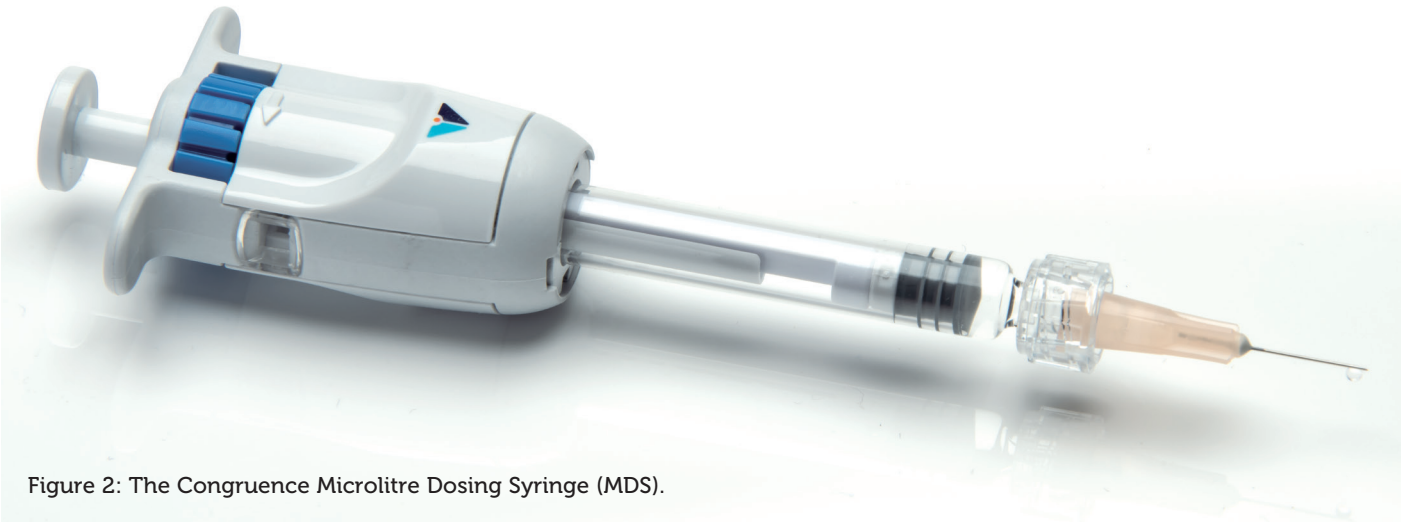

Figure 2: The Congruence Microlitre Dosing Syringe (MDS).

"The MDS was evaluated by 30 retina specialists from the US, Europe, Japan and Latin America to demonstrate error-free use, in addition to accurate, precise microlitre delivery."

long PFS. A prefilled, pre-set, single-use system is shown in Figure 2. The steps of use include:

- Attaching a needle
- Setting the dose (by rotating a dose dial)
- Depressing the plunger rod to inject.

In this variant, the dose is set at time of manufacturing and the user cannot set and deliver a different dose volume. Addition of the device subassembly to the filled PFS can be either manual or automated.

Depending on the application, the MDS platform can be modified to yield the following possible configurations:

- Prefilled and pre-set
- Prefilled and user-set
- User-filled and pre-set
- User-filled and user-set.

Both user-filled configurations allow a syringe integrated with the MDS to be packaged with a drug vial. The user-filled, user-set MDS configuration provides accurate and precise microlitre dosing with functionality equivalent to a conventional syringe. The MDS can also be customised to accommodate differences in drug viscosity, dose volume, look and feel, and PFS size/type. While the MDS can work with 0.5 mL PFS, compatibility with a 1 mL long PFS provides pharmaceutical and biotechnology companies a lot of flexibility, not only with PFS component sourcing but also with drug filling.

The inbuilt mechanical advantage of the MDS with a 1 mL long PFS enables delivery of a drug solution with viscosity of up to 100 cp with an injection force of less than 30 N when injecting through a 30G, half-inch long needle.

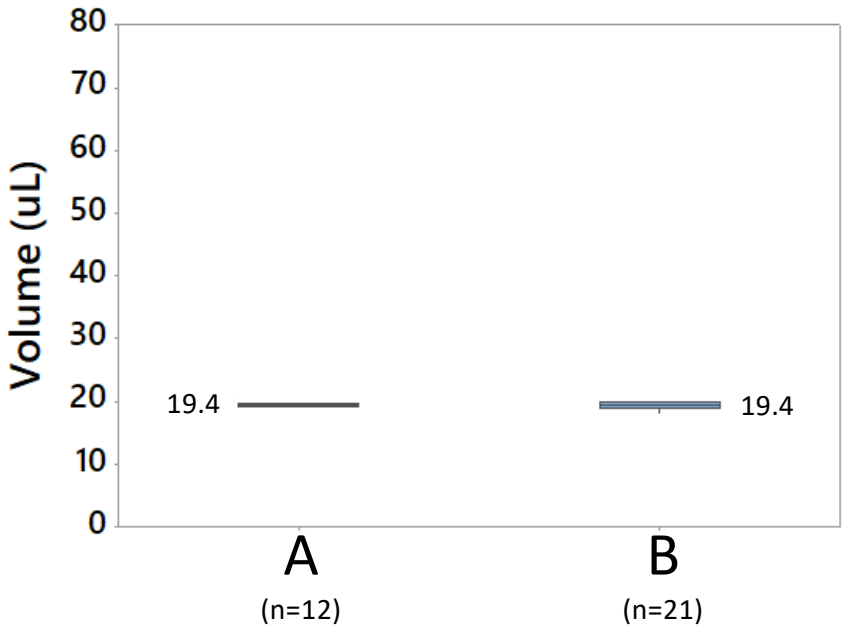


Figure 3. User data with MDS for a 20 µL dose using a 1 mL long PFS showing measured dose in laboratory setting (A), and measured dose for 21 users (B).

## USER EVALUATION OF THE MDS

The MDS was evaluated by 30 retina specialists from the US, Europe, Japan and Latin America, to demonstrate error-free use, in addition to accurate, precise microlitre delivery (Figure 3). The user data compares favourably with data generated in the laboratory, illustrating that MDS performance is independent of the user. Other key highlights from the user evaluation included:

- 100% of the respondents were able to perform all steps of operation in an error-free manner.
- 87% of the respondents would prefer to use the MDS over other currently available options.
- 97% of the respondents indicated that they found the device comfortable to use.
- 90% of the respondents indicated that they found the device easy to use.
- The dose time was comparable with Lucentis® PFS.

The MDS with a 1 mL long PFS outperformed conventional hypodermic

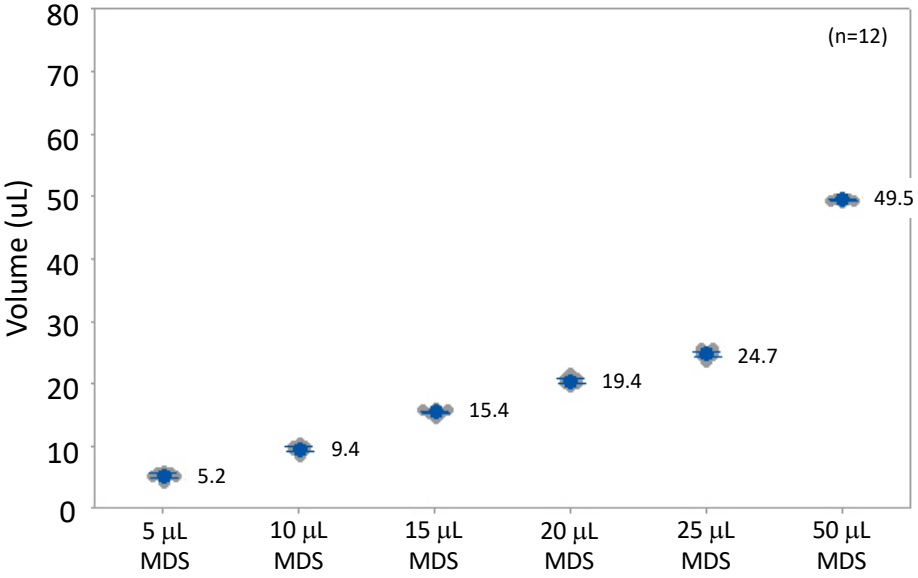


Figure 4: Various dose levels delivered using the MDS with 1 mL long PFS demonstrating accuracy and precision (average values shown).

syringes and 0.5 mL PFS. The open architecture of the MDS allows pharmaceutical and biotech companies to source syringe container closure components from their syringe or elastomer suppliers of choice. The MDS allows seamless integration with standard pharmaceutical fill-finish infrastructure and components despite the challenging dosing requirements in this therapeutic area.

Since the MDS is a metered dose delivery system, the accuracy of the delivered dose is not dependent on accuracy of drug fill volume, as long as there is sufficient drug fill to account for dead space in the syringe and needle the correct dose will be delivered. Break-loose force also has no impact on the performance of the MDS.

## MDS DOSE RANGE, COST SAVINGS DURING DRUG DEVELOPMENT

The MDS has been shown to be able to deliver a dose as low as 5 µL accurately (Figure 4) using a 1 mL long PFS. This capability allows for cost-effective dose-ranging studies. Pharmaceutical development requires demonstration of a dose-response. The drug material costs scale by the number of drug dose levels to be evaluated. The MDS can enable significant savings by requiring preparation of only one drug solution at its highest strength, with delivery of lower levels being achieved by adjusting the volume delivered. Previously, this was not possible because of the difficulty of reliably delivering accurate microlitre doses. Additionally, improving clinical trial design by modulating device-use parameters to ensure masking can easily be engineered with the MDS.

## MDS PRESENT STATUS & FUTURE OUTLOOK

The MDS will be available for clinical evaluation and use in 2019.

Congruence Medical Solutions is developing other technologies relevant to the development and delivery of pharmaceutical agents for ophthalmic applications. For example, a device for accurately and precisely injecting extremely viscous drug formulations (>1000 cp) with a standard PFS is under development. Additionally, Congruence has developed a device for preclinical applications to inject drug volumes as low as 0.5 µL accurately by extending the capability of the MDS.

## ABOUT THE AUTHOR

**Gautam Shetty** is the founder of Congruence Medical Solutions. Prior to Congruence, he was General Manager of a Novel Drug Delivery Systems business unit. He pioneered development of ophthalmic drug delivery devices and targeted organ delivery systems. Prior to that, he held a number of positions at BD, involving R&D, strategic marketing, commercialisation planning and M&A. Dr Shetty holds a PhD in Biomedical Engineering from Case Western Reserve University. He has authored more than 12 patents in the injectable drug delivery device space covering ocular drug delivery systems, pen injectors and patch pumps.

## ACKNOWLEDGEMENTS

The author would like to acknowledge the contributions from Lou Castanga, of CAE Consulting, and Lance Wetzel, Independent Consultant.

## ABOUT THE COMPANY

Congruence Medical Solutions, LLC is a science-based, technical innovation company focused on the development and supply of ophthalmic drug delivery devices.

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KEDALION THERAPEUTICS

# ACUSTREAM™: BRINGING TOPICAL OPHTHALMIC DRUG DELIVERY INTO THE MODERN ERA

In this article, Peter Noymer, PhD, Chief Executive Officer, Ehud Ivri, Chief Technology Officer and Co-founder, Reynaldo Quintana, Vice-President of Engineering, and Mark Blumenkranz, MD, Executive Chairman and Co-founder, introduce AcuStream, a novel device for next-generation delivery of topical ophthalmic delivery via an aim-assisted stream.

## INTRODUCTION

Virtually all topically administered ocular therapies are delivered by a standard eyedropper, requiring the patient to tilt their head back and administer a prescribed number of drops into their eye one or more times per day. This method is woefully out of date, with:

- More than 90% of patients dosing improperly
- 24% of eyedrop bottles being contaminated[1]
- 30% of patients who think they have good technique actually missing the eye.[2]

This is not modern medicine.

Standard eyedroppers also end up delivering a dose four or five times larger than the tear film of the eye can retain, meaning that more drug than necessary is being dosed compared with what is actually required to treat a given condition. The majority of the delivered formulation is often washed out of the eye or even misses they eye entirely because of poor delivery technique. This overdosing can also cause systemic adverse events if the drug enters the systemic circulation in high enough quantities. For example, the beta blocker timolol, used in the treatment of glaucoma, has been documented to have potential cardiac or pulmonary complications in high risk populations if it reaches high enough systemic concentrations after conventional topical administration. And any excess drug product remaining in the eye may lead to local adverse events. For example, prostaglandins can cause conjunctival hyperaemia, increased pigmentation of the iris, or abnormal eyelash growth.

Dosing five times more than the therapeutic dose is also wasteful of drug product. In mass markets, with the wastage multiplied across millions of doses per year, the cumulative cost on the healthcare system can grow very quickly, even for lower-cost APIs. Clearly, a system that could administer much less active ingredient and only what is needed both more accurately and comfortably would be highly desirable from both a clinical and an industrial point of view.

Patients have demonstrable difficulty properly using traditional eyedroppers. These difficulties lead to deficiencies in both compliance, whereby patients administer

> "Patients hold AcuStream in front of their eye rather than above it, greatly increasing not only comfort and ease-of-use but crucially also increasing dose precision and accuracy."

**Dr Peter Noymer**
Chief Executive Officer

**Mr Ehud Ivri**
Chief Technology Officer and Co-founder

**Mr Reynaldo Quintana**
Vice-President of Engineering

**Dr Mark Blumenkranz**
Executive Chairman and Co-founder

**Kedalion Therapeutics, Inc**
1490 O'Brien Drive, Suite C
Menlo Park
CA 94025
United States

**www.kedalionthera.com**


Figure 1: Kedalion's AcuStream device for delivering topical front-of-the-eye ophthalmic medication.

"AcuStream delivers less drug to achieve the same effect, meaning that there is less drug wasted and that drugs delivered by AcuStream could result in fewer adverse events than standard eyedroppers."

the wrong number of drops (exacerbating the existing issue of too much drug product being delivered) or fail to target the eye properly, and adherence, meaning patients are put off continuing their therapy due to discomfort, adverse events, inconvenience or other issues.

There is a clear, unmet need in the ophthalmology market for an improved, efficient modern delivery system.

## ACUSTREAM, THE NEXT STAGE OF TOPICAL OPHTHALMIC DELIVERY

Kedalion Therapeutics is a venture-backed, clinical-stage ophthalmology company based in Menlo Park, CA, US. Kedalion aims to meet this unmet need in topical ophthalmic drug delivery and to transform the topical ophthalmology market with its proprietary AcuStream™ delivery system for topical ocular treatments (Figure 1). AcuStream is a proprietary device for easy, accurate and precise dosing, which is achieved using a novel dispensing mechanism. AcuStream administers a topical formulation directly to the surface of the eye without patients tilting their heads back and with a proprietary aiming mechanism to improve accuracy of delivery. Patients hold the device in front of their eye rather than above it, greatly increasing not only comfort and ease-of-use but crucially also increasing dose precision and accuracy with the novel aiming and dispensing mechanisms.

Human factors design played a significant role in the creation of AcuStream. A major contributor to the difficulties in ensuring patient compliance with topical ophthalmic treatments is the discomfort patients experience with traditional eyedrops, having to crane their heads back and to try to line up the dropper directly above their eye. In addition, an exaggerated blink reflex and lid spasm could block the administration of the drop or cause the medication to be ejected from the surface of the eye. The proprietary aiming and delivery mechanisms in AcuStream allow straightforward dosing, meaning that patients apply their topical medication while looking directly forward, a more natural position that engenders greater accuracy and comfort, and therefore better compliance (Figure 2). The aiming technology makes it easy for patients to ensure that their ophthalmic medication is delivered directly to the eye, and the dispensing technology ensures that the proper dose is administered reproducibly.

This novel approach can also improve adherence. Because the dose is reliably and precisely delivered, AcuStream delivers less drug to achieve the same effect, meaning that there is less drug wasted and that drugs delivered by AcuStream could result in fewer adverse events than standard eyedroppers. This, combined with enhanced comfort and ease-of-use, means that patients may have more incentive to adhere to an AcuStream treatment regimen compared with standard eyedroppers.

This is especially important for a chronic condition such as glaucoma, for example. When it comes to treating glaucoma, healthcare providers have a broad array of increasingly invasive treatments for managing intraocular pressure (IOP), starting with simple topical drug formulations before moving up to stents and possibly even surgery. Therefore, if a patient has compliance and adherence issues with their initial topical treatments, it increases the probability that IOP will not be well-managed and that more drops would have to be prescribed to try to manage IOP before moving on to increasingly invasive, surgical treatments.

Figure 2: AcuStream delivers medication directly to the eye in a stream with the patient looking directly forward, assisted by a proprietary aim-assisting mechanism.

AcuStream's clear benefits position it for success in the topical ophthalmic market, in the treatment of conditions such as glaucoma, dry eye, uveitis, allergic disease and infections. Additionally, the regulatory pathway to approval for AcuStream combined with approved drugs can follow streamlined processes such as the US FDA's 505(b)(2) approval pathway. Because of its novel design and mode of use, AcuStream is not only applicable for optimal delivery of existing therapies as differentiated products or for lifecycle management, but it could also change the landscape for new molecular entities (NMEs) in the topical ophthalmic space by creating a new paradigm for dosing and treatment.

AcuStream's precision dispensing mechanism uses an IP-protected architecture and is compatible with existing pharmaceutical manufacturing processes to minimise disruption and facilitate easy adoption as the topical ophthalmic delivery device of choice. Underlying the novel delivery system, AcuStream uses traditional drug container materials manufactured using standard aseptic fill-finish processes, thus making it easier to adopt AcuStream and integrate it into existing low-cost industrialisation processes.

## Promising Phase I Clinical Trial Results

In 2017, Kedalion conducted two clinical trials comparing AcuStream with standard eyedroppers.

The first trial measured pupil dilation following administration of a tropicamide-phenylephrine combination formulation (1% tropicamide solution combined with 2.5% phenylephrine solution). The study comprised 40 doses in 20 patients, each treated using a single AcuStream dose in one eye and a single standard eyedropper dose in the other eye (randomised for left eye and right eye). As shown in Figure 3, AcuStream achieved a statistically similar dilation effect while using a 70% lower dose. AcuStream was also shown to be 45% more comfortable and resulted in 35% fewer adverse events.

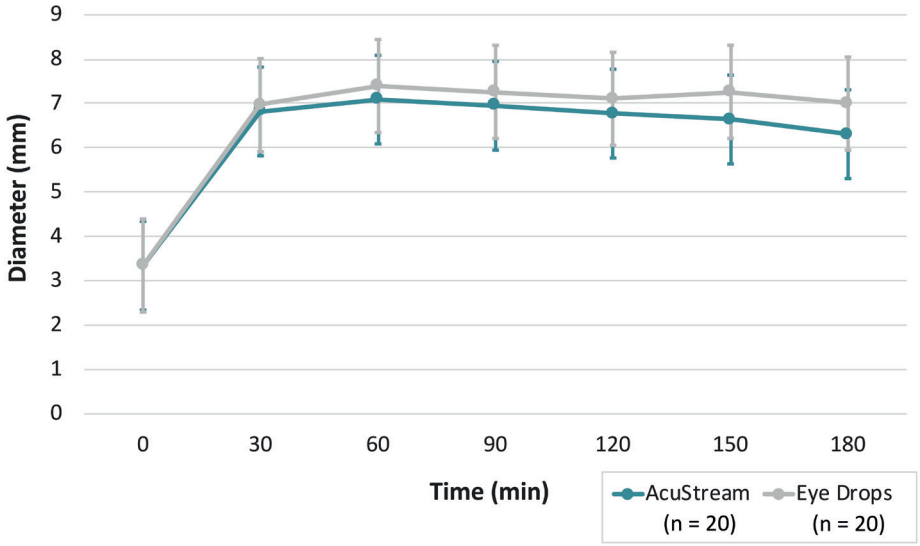


Figure 3: Phase I dilation results – AcuStream versus standard eyedropper tropicamide-phenylephrine.

The other trial measured IOP in glaucoma patients following administration of latanoprost. The study comprised 36 doses in 18 patients with ocular hypertension or glaucoma already under topical oculohypotenisve therapy. Patients first underwent a washout of existing topical medication for a minimum of one month and then were randomised to be treated using either a single AcuStream dose in both eyes of latanoprost 0.005% or a single standard eyedropper dose in both eyes of latanoprost 0.005%. As shown in Figure 4, the AcuStream cohort achieved a statistically similar effect in IOP reduction while using a 70% lower dose compared with the eyedropper cohort.

Both trials very clearly demonstrated proof-of-concept for the effectiveness and improved comfort, convenience and safety of the AcuStream delivery system.

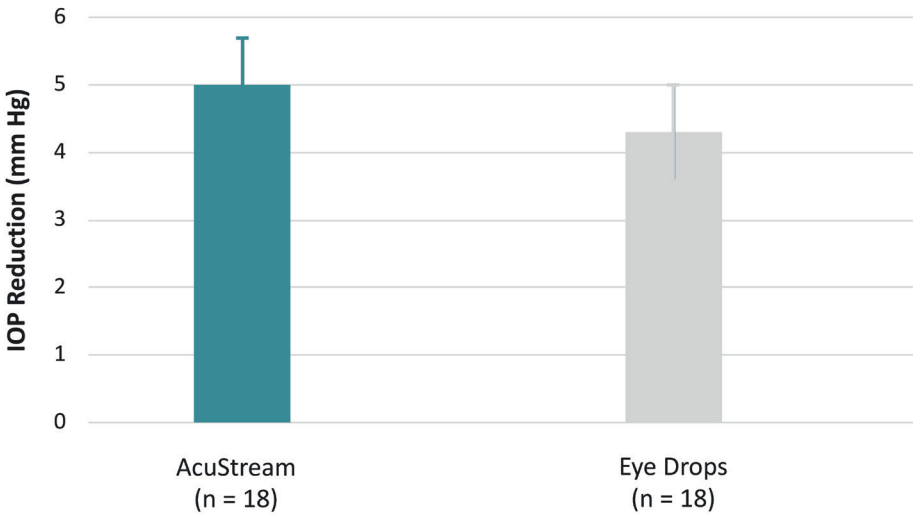


Figure 4: Phase I glaucoma results – AcuStream versus standard eyedropper latanoprost.

## WHERE TO NEXT?

Since being founded in 2015, Kedalion Therapeutics has progressed rapidly to become a clinical-stage topical ophthalmic product company, having completed two successful Phase I trials. Phase II studies are planned for mid-2019 and initial marketing applications and approvals are anticipated in the 2021/22 timeframe.

In addition to the pipeline of drug products, Kedalion anticipates being able to offer different platform features as needed to meet patient needs in different therapeutic areas. Such features are expected to include connectivity elements to support digital health initiatives as well as container closure system that could allow preservative free formulations to be provided in a multi dose format.

> "AcuStream is strongly IP-protected with patents extending out to 2032 and beyond."

AcuStream is strongly IP-protected with patents extending out to 2032 and beyond. Kedalion is establishing a proprietary product pipeline based on AcuStream. In addition, AcuStream presents the opportunity for partnerships with the means to expand the ability to offer patients a comfortable, convenient and effective ophthalmic delivery system fit for the modern age. AcuStream has the potential not only to make topical ophthalmic medicines stand out from competitors, but also to enhance them by making them more patient friendly, increasing adherence and compliance, and additionally reducing drug product wastage.

Importantly, in addition to the prescription pharmaceutical market, AcuStream also has the potential to move into over-the-counter (OTC) ophthalmics market. Its distinctive novel delivery method, patient-centric design and fast regulatory pathway make it an ideal candidate for OTC medications.

## CONCLUSION

Kedalion's AcuStream device is set to revolutionise topical ophthalmic delivery across multiple indications. The patient-friendly device delivers medication accurately and precisely in a straightforward stream that is easy to aim and matches the efficacy of standard eyedroppers but using up to 80% less drug product. With a streamlined route to regulatory approval available for existing drugs, very low cost-of-goods, compatibility with existing pharma manufacturing processes, and its ability to distinguish itself in a market ripe for innovation, AcuStream offers a clinically and commercially attractive opportunity for a differentiated ophthalmic product portfolio.

## ABOUT THE AUTHORS

**Peter Noymer** is Chief Executive Officer of Kedalion Therapeutics and has more than 20 years of experience in research, development and commercialisation of pharmaceutical products with novel delivery technologies. Before joining Kedalion, he was Chief Operating Officer at SteadyMed Therapeutics, focused on developing novel products with the PatchPump™ technology. Earlier, Peter was Vice-President of Product R&D at Alexza Pharmaceuticals, where, during his time there, the company obtained US and EU approval for Adasuve®(loxapine), the first inhalable treatment for agitation associated with schizophrenia or bipolar I disorder. Prior to Alexza, Dr Noymer held various management positions at Aradigm Corporation. He received MS and PhD degrees in engineering from MIT, and a BS degree in engineering from Princeton University.

**Ehud Ivri** is Kedalion's Chief Technology Officer and Co-founder. He is an electro-mechanical engineer specialising in microfluidics and piezo-electronics, focused mainly in the field of drug delivery. He holds over 40 patents related to medical devices and drug delivery systems. Mr Ivri's work in the medical device field began with his founding of Aerogen, now a leading producer of nebulisers for inhalable drug delivery. More recently, he developed a new micro-dispensing technology for the production of DNA micro-arrays that was licensed to BioDot. Mr Ivri holds an MS in Mechanical Engineering from the Technion-Israel Institute of Technology.

**Reynaldo Quintana** is Kedalion's Vice-President of Engineering. Prior to Kedalion, he was Senior Director of Global Engineering at Fontem Ventures, and also led device development at Alexza Pharmaceuticals. Mr Quintana also held management positions with NJOY, ZOLL Medical, Aerogen and IDEO, and consulted to Sunovion Pharmaceuticals, Genentech and Elevation Pharmaceuticals. He is an inventor or co-inventor on 18 biomedical patents. He received a BS in Mechanical Engineering from the University of Maryland, a BS in Physics from Frostburg State University and an MS in Biomedical Engineering from The Catholic University of America.

**Mark Blumenkranz** is Kedalion's Executive Chairman and Co-founder, a noted serial entrepreneur and the Managing Director of Lagunita Biosciences. Dr Blumenkranz is also the HJ Smead Professor Emeritus of Ophthalmology at Stanford University and was departmental Chairman from 1997 to 2015 and the founding director of the Byers Eye Institute. He was a Founder and Director of Macusight, Peak Surgical, Optimedica Corporation, Adverum Biotechnologies, Oculeve and Digisight Corporation (now Verana Heath). He has also served on the Boards of Directors of a number of other private and publicly traded ophthalmic drug and medical device companies including Oculex Pharmaceuticals, OIS, Midlabs, Presbia, and Beaver-Visitec (BVI Inc). He completed the Stanford Executive Program in the Graduate School of Business in 2004 and received his undergraduate, Masters in Biochemical Pharmacology, and MD from Brown University (AOA), where he is a Fellow of the Corporation and Immediate Past Chair of the Medical School Committee.

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# USER TESTING: CRITICAL FOR TRULY UNDERSTANDING PATIENT NEEDS

Here, Fanny Sellier, Global Category Manager, Ophthalmic Products, Nemera, presents a trio of comparative user studies between Nemera's Novelia® preservative-free, multidose eyedropper and similar products from competitors, highlighting the need for user studies in addition to standard *in vitro* tests when assessing the quality of an ophthalmic drug delivery device.

## INTRODUCTION

Ophthalmic pathologies include eyesight threatening conditions (diabetic retinopathy, glaucoma, cataract, age-related macular degeneration and retinal detachment) and, relatively speaking, less serious eye conditions (dry eye, red eye, etc), all of which are treated by ocular injections, eyedrops or surgery. Eyedrops are primarily used for glaucoma, dry eye disease (DED), conjunctivitis and allergy. For chronic diseases, when daily treatments are needed, preservative-free formulations are key to protecting the patient's ocular surface, as preservatives can cause allergic reactions, irritations and can even damage patients' eyes.[1] Thus, preservative-free formulations are needed for glaucoma and DED.

At present, two options are available for dispensing preservative-free ophthalmic formulations: unit-dose systems or preservative-free, multidose systems. Unit-doses are generally considered to be not patient-friendly, and are often costly and bulky, making them unsuitable for home use for chronic conditions.[2] Therefore, in order to improve patient compliance and limit waste, the preferable solution is to use preservative-free formulations with the convenience of a multidose bottle. Two main types of preservative-free, multidose (PFMD) systems exist today:

- **Pump systems** – These use either an airless container or a filter technology to allow air to enter back into the bottle. The advantage of pump systems is that the dose is controlled and consistent, however priming is needed before delivering the first dose.
- **Squeeze bottles** – These dispense drops using either a non-return valve or a filtering system. Most of them also rely on an air filtering system to stop bacteria entering the bottle when it is open to the air. There is no priming with squeeze bottles, but the dose is less controlled.

Eyedropper performance is mainly evaluated by *in vitro* tests, such as the dose variability against shelf life, the sterility of the content and the delivered drop. Despite these important *in vitro* tests, the usability aspects of the drug delivery system are not fully considered. Therefore, also conducting a user test evaluation is key because, even if it is successful according to the *in vitro* tests, an eyedropper may not necessarily be appreciated by patients due to poor usability. Consequently, a device with good *in vitro* test performance could be clinically inefficient.

In this article, we report on three user tests that have been conducted to evaluate the level of difference in terms of usability characteristics and user preferences for different PFMD systems.

## COMPARATIVE USER STUDY 1: NOVELIA® BOTTLE & 3K®

A randomised study was conducted at the end of 2017 at the Department of Ophthalmology, Kuopio University Hospital (Kuopio, Finland), interviewing 30 patients over 50 years old with either glaucoma or ocular hypertension, with a majority of female participants (77%).[3] The patients used safety glasses and instilled eyedrops from two different PFMD systems: the Novelia® bottle from Nemera and the

**Fanny Sellier**
Global Category Manager,
Ophthalmic Products
T: +33 4 74 94 06 54
E: fanny.sellier@nemera.net

**Nemera**
20, Avenue de la Gare - B.P. 30
38292 La Verpillière Cedex
France

**www.nemera.net**

3K®-System pump from Ursatec (St Wendel, Germany). The participants were asked to rate several parameters from -5 (extremely difficult) to +5 (extremely easy):

- Opening of the container
- Squeeze force needed for drop administration
- Targeting the eye
- Drop control
- Removal of the residual drop
- General usability of the container.

In addition, the users were also asked about their preference between the two eyedrop containers.

According to the results, Novelia® outperformed 3K® in the tasks of opening, squeezing, targeting the eye and removing the residual drop, as well as having better general usability (Figure 1). 100% of users were able to open the Novelia® bottle and deliver a singular drop onto the protective glasses. Five participants did not succeed in opening the 3K® system and seven out of the remaining 25 were not able to instil a singular drop onto the safety glasses. 97% of users named Novelia® as their first choice container over the 3K® system, with only one participant in favour of 3K®.

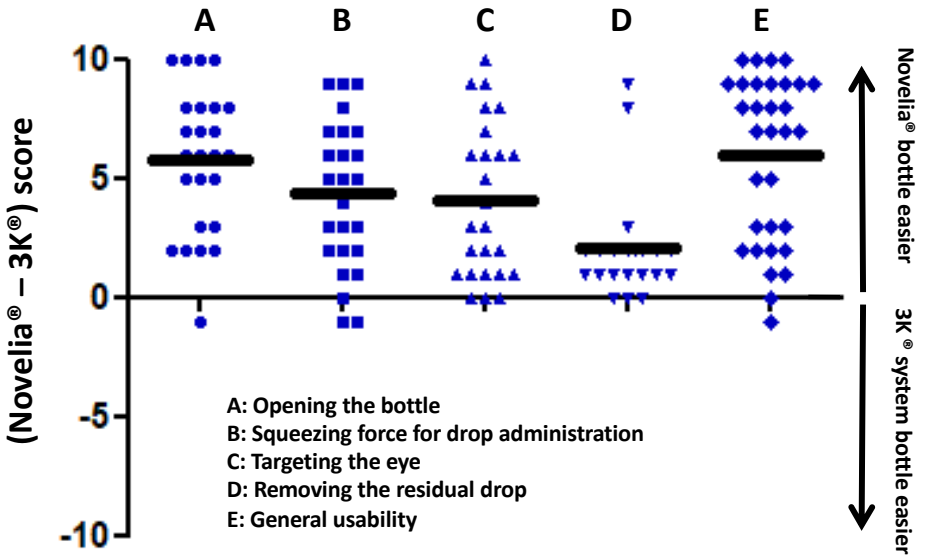


Figure 1: The difference between scores given by 30 patients with glaucoma or ocular hypertension for Novelia® and 3K®-System bottles (Novelia® - 3K®) . Adapted from Figure 1 of the study "Preferences and ease of use of preservative-free IOP-lowering eyedrop containers: A comparison of two multidose bottles" with the permission of Clinical Investigation journal.

## COMPARATIVE USER STUDY 2: NOVELIA® BOTTLE & OSD

A second randomised study was performed for Nemera by the independent user studies consultancy GfK (Suresnes, France).[4] This study comprised 90 patients (40 in Europe and 50 in the US). 75% of them were over 60 years old. 40% of the participants had glaucoma, 40% were regular users of eyedrops (primarily for DED) and 20% were occasional users (for example for conjunctivitis). The interviews happened at the respondents' homes or in GfK's offices, where patients instilled eyedrops (using safety glasses) with different eyedroppers and rated these systems on nine attributes from 1 (very poor) to 5 (very good). Both ophthalmic systems were PFMD bottles: The Ophthalmic Squeeze Dispenser (OSD) from Aptar Pharma (Radofzell, Germany) and Novelia® from Nemera.

Based on the results, Novelia® was found to display superior usability characteristics, with the exception of the grip of the bottle, where both devices were considered to be the same (Figure 2).

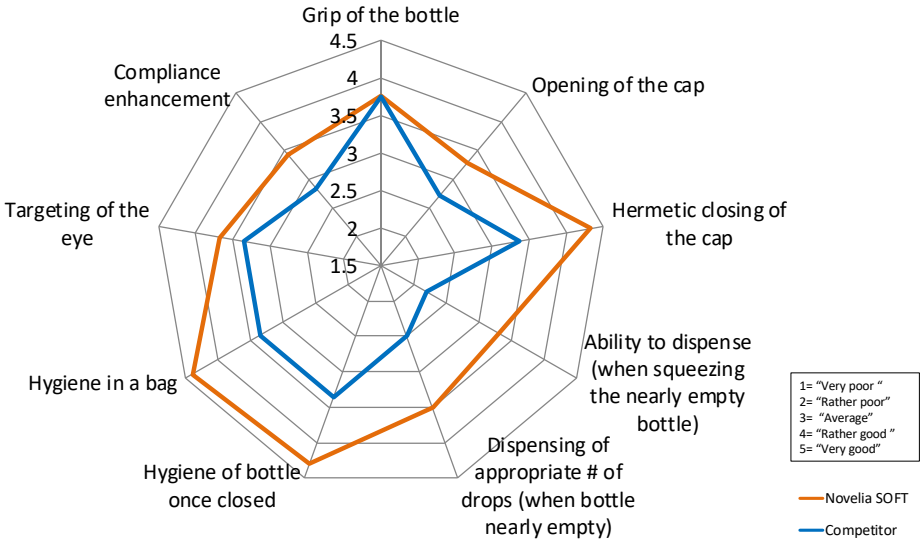


Figure 2: Mean scores across different parameters given by 90 patients with glaucoma, dry eye or conjunctivitis using Novelia® and OSD.

First of all, the screw cap on Novelia® proved intuitive, as it is a similar mechanism to that found on regular, preservative-containing three-piece eyedroppers, whereas the OSD cap opening was not perceived as obvious or easy. Patients are not used to snap-on caps with their current bottles, and so found opening the OSD confusing. Additionally, some patients found it too loose after repeated use, meaning it ceased to seal hermetically and could come off when carried in a purse or bag. The robustness of the Novelia® screw cap made patients feel more comfortable when carrying it in a bag as it felt more secure.

The biggest difference between both systems was seen when the bottle was nearly empty at the end of use, at which point the participants found squeezing the OSD bottle harder than the Novelia® one.

Additionally, participants appreciated the Novelia® blue tip as it helped them target their eyes.

Overall, 68 out of 90 users (76%) preferred Novelia® over the OSD.

## COMPARATIVE USER STUDY 3: NOVELIA® BOTTLE & 3K®

The third randomised study sponsored by Nemera was conducted early in 2018 in Marketing Espace's office (Lyon, France).[5] Out of the 20 users interviewed, 60% were regular users of eyedrops (including seven with glaucoma) and 40% were occasional users. The participants were asked to administer drops onto protective glasses with

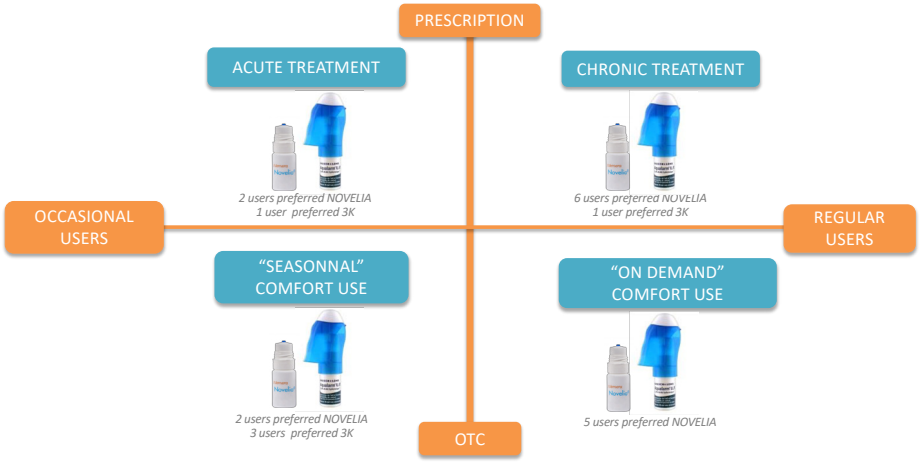


**Figure 3: User preference segmented by user type (regular/occasional) and treatment type (medical with prescription/comfort) on 20 patients.**

the same two PFMD containers as the first study: Novelia® and the 3K®-system. They also selected their preferred system overall and rated them from 1 (very poor) to 5 (very good) on several individual parameters:

- Cap opening
- Ease of first time use
- One drop at a time
- Targeting the eye
- Hermetic sealing
- On-the-go use
- Ease of treatment adherence.

Overall the 3K®-system was rated at 3.4/5 (average/good) and Novelia at 4.2/5 (good). Patients reported that Novelia® was easy to use and ideal for an on-the-go use. Novelia® also outperformed 3K® by 0.6 or 0.7 points on cap opening, hermetic sealing and eye targeting. Both systems performed equally (3.7/5) on one drop at a time. 75% of users preferred Novelia® over 3K® for these reasons.

Another interesting finding was that regular and occasional users don't have the same preferences for eyedrop containers and value them differently. On the one hand, both systems were appreciated similarly by occasional users, four of eight occasional users preferred Novelia® and the same number preferred 3K®. On the other hand, regular users demonstrated a very strong preference for Novelia®, with 11 of 12 regular users preferring Novelia®. This would suggest that chronic users are more sensitive to easy-to-use features.

## CONCLUSION

The three studies demonstrated a significant difference between PFMD systems in terms of usability, which can have an impact on patient adherence and treatment efficacy. The studies were conducted in hospitals, patients' homes and offices. Participants had glaucoma, ocular hypertension, DED, conjunctivitis and allergies. The studies did however have some limitations due to the low number of participants and two of them being sponsored by Nemera. However, they all point towards a patient preference for the same PFMD system, Novelia®, highlighting the difference between the ophthalmic systems tested.

The third study highlighted a difference in patient preference according to the frequency with which they use the eyedropper. Notably, patients with chronic diseases, such as glaucoma and DED, show a strong preference for a product that is easy to use daily and easy to carry. Glaucoma patients are often elderly people and have difficulties using eyedroppers but still need to administer eyedrops every day, sometimes twice daily. Nearly nine out of 10 glaucoma patients are unable to instil eyedrops correctly,[6] and therefore an easy-to-use system that is appreciated by patients could contribute to improving their compliance to a treatment.

In conclusion, drug delivery systems should be assessed not only in terms of *in vitro* performance (drop consistency, leachables, etc) but also in terms of patient usability.

## 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; and 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.

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## ABOUT THE AUTHOR


**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.

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# TRENDS IN ANTI-GLAUCOMA TOPICAL TREATMENTS

**In this article, Rouven Kraus, International Sales, Aero Pump, discusses the rising incidence of ophthalmic disorders worldwide. Furthermore he presents the case for multidose delivery systems rather than single-use disposables, and introduces Aero Pump's Ophthalmic Multidose System which utilises their proprietary 3K®-technology for preservative-free, multidose eyedroppers.**

The ophthalmic drug market is one of the fastest growing market sectors in the pharmaceutical industry. More than 285 million people suffer from visual impairments worldwide, a number expected to rise due to the increasing prevalence of ophthalmic disorders. Such disorders are on the rise primarily because of extended life expectancy in developed countries (ageing populations), increased air pollution and higher numbers of patients being diagnosed with diabetes.

A total of 962 million people globally were aged 65 years or over in 2017, however, the number of people in this age bracket is expected to nearly double by 2050 – a total of 1.6 billion people. 5% of people aged 65 or over develop glaucoma, a group of optic neuropathies resulting from damage to the optic nerve caused by intraocular pressure. Glaucoma is the second leading cause of irreversible blindness. With a predicted 80 million people affected by glaucoma by 2020, it will be one of the most prevalent ocular diseases.

Drugs are usually the first line of treatment for primary open-angle glaucoma (POAG), the most common type of glaucoma. Alpha agonists like brimonidine decrease the production of aqueous humour and increase uveoscleral outflow. Beta blockers (e.g. timolol) and carbonic anhydrase inhibitors (e.g. dorzolamide, brinzolamide) decrease the aqueous humour through the ciliary body, whereas miotics (e.g. pilocarpine) and prostaglandin analogues (e.g. latanoprost, bimatoprost, travoprost) improve the drainage. Rho khinase inhibitors (e.g. netarsudil) are a new class of glaucoma drugs, first launched in 2018. Rho khinase inhibitor eyedrops reduce the elevated intraocular pressure (IOP) by suppressing the rho khinase enzymes that produce the aqueous humour.

> "The launch of novel anti-glaucoma drugs with additional neuroprotective properties that avoid loss of retinal ganglion cells is set to become a major breakthrough in glaucoma treatment."

Of these, prostaglandin analogues are the standard first-line treatment to decrease IOP due to their advantage of greater efficacy. Manufacturers have launched combination products that combine prostaglandin analogues with a beta-blocker, which are predominantly to be used once or twice a day.

Single-use vials (often produced in the blow-fill-seal technology) do not protect the contents from contamination after they are opened, meaning the patient needs to

**Rouven Kraus**
International Sales
T: +49 6146 6030
E: sales@aeropump.de

**Aero Pump GmbH**
Dr-Ruben-Rausing-Straße 5
65239 Hochheim
Germany

**www.aeropump.de/en/home**


Figure 1: Thea Pharma's Duokopt containing dorzolamide and timolol in the 3K®-system and the ergonomically designed Easygrip®, which enables a safe grip and an easy administration of the drops for the patient.


Figure 2: Bausch + Lomb's Vizitrav® containing Travoprost in the 3K®-system.

"Aero Pump GmbH, together with its partner URSATEC Verpackung GmbH, have developed a preservative-free, multidose system with their proprietary 3K®-technology."

discard them after the administration of just one dose. Patients often do not follow those instructions and use their single-use vials more than once. As such, the superior option would be to use multidose containers, which enable repeated use of the product to deliver the required dose daily.

The industry has been challenged to design multidose eyedroppers which satisfy all the regulatory guidelines set out by the authorities. The EMA recommends sterile eyedrops to be preservative-free, as it is known that preserving agents cause side-effects like irritation of the ocular surface, and to dispense a defined metered dose with each drop.

Preservative-free, multidose systems either have an airless container like the COMOD®-system or require a special sinter filter with antimicrobial properties to compensate for the vacuum formed inside the container after the drop is dispensed, as well as a valve that forms a microbiologically tight seal (e.g. the 3K®-technology in Aero Pump's Ophthalmic Multidose System).

Due to the expiry of patents relating to anti-glaucoma products in the past few years, many generic products with a prostaglandine analogue are currently in development. Based on the latest guidelines, those manufacturers are often looking to launch their products in preservative-free, multidose containers.

The launch of novel anti-glaucoma drugs with additional neuroprotective properties that avoid loss of retinal ganglion cells is set to become a major breakthrough in glaucoma treatment. Currently, numerous clinical trials are taking place, combining formulations with the benefits of using just one bottle for several medications. For glaucoma patients and ophthalmologists, it is an exciting time as these new medications promise improved features by directly targeting the trabecular meshwork.

## AERO PUMP'S PRESERVATIVE-FREE OPHTHALMIC MULTIDOSE SYSTEM

Aero Pump GmbH, together with its partner URSATEC Verpackung GmbH, have developed a preservative-free, multidose system with their proprietary 3K®-technology (Figures 1 and 2). Special germ-reducing components inside the 3K®-system ensure the microbiological integrity and safety of the device. This pump system is available for use with plastic or glass containers and, in terms of reducing container interaction with the product, this is a particular advantage.

The 3K®-system delivers an accurate dose across the full lifecycle of the product, with one measured drop per actuation. Conventional squeeze-actuated devices on the other hand are known to have an imprecise dose accuracy, some can even create an extremely uncomfortable jet when squeezed.

The actuation force of Aero Pump's Ophthalmic Multidose System is stable and independent of the residual liquid inside the container. This fact is especially noticeable for older patients where it can be very

"The actuation force of Aero Pump's Ophthalmic Multidose System is stable and independent of the residual liquid inside the container. This fact is especially noticeable for older patients where it can be very difficult to eject the last few drops of the liquid."

Figure 3: The Ophthalmic Multidose System in different sleeve designs.

difficult to eject the last few drops of the liquid, which can often lead to an increased residual volume when squeeze-actuated devices are used.

Alongside the development of ophthalmic multidose devices, Aero Pump has developed various customer-friendly actuation aids that enable a convenient application of the drop into the eye of the patient (Figure 3).

## ABOUT THE COMPANY

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 ophthalmic, nasal, buccal and topical fields, suitable for preserved and preservative-free OTC and prescription drugs.

## ABOUT THE AUTHOR

**Rouven Kraus** has over 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 the sales coordination of the European, Middle East, Far East and the local Maghreb market as well as the strategic approach to new ophthalmic developments and delivery technologies. Recently he assumed responsibilities for opening up the US and Canadian market for Aero Pump.

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| Glass Type-I | 5ml, 10ml |

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# USING MARKET RESEARCH TO CREATE A PRESERVATIVE-FREE MULTIDOSE EYEDROPPER

An ageing population, high computer and mobile device use and increasing pollution and allergies are all contributing to a greater global demand for eyedrops. At the same time, the move towards preservative-free formulations is driving the development of novel ophthalmic devices. Thomas Grinnan, Vice-President, Sales & Marketing, Healthcare, and Ralf Hergenröther, Product Line Manager, Healthcare Solutions, both of Silgan Dispensing Systems, explain how extensive market research and consumer testing led to the development of an eyedropper that meets patients' and physicians' needs for an easy-to-use device, which offers precise dosing and anti-microbial integrity.

Ophthalmic health is becoming an ever more significant issue due to factors such as the continued growth of urban populations, an ageing population and a rise in the levels of particulate matter in the air. In 2017, the global ophthalmic drug market revenue was US$24 billion (£19 billion).[1] By 2021, it's expected to be $28 billion, with retinal disorder, allergies, glaucoma and dry eye disease (DED) among the biggest categories fuelling the growth. Also driving market expansion is the fact that some of the diseases that require the use of eyedrops are chronic.

## PRESERVATIVE-FREE PACKAGING

While ophthalmic medicines are traditionally packaged using preservatives, and primarily still are in the US, there is currently a push in Europe towards using preservative-free (PF) packaging, following research which suggested that preserved eye medications can be harmful to the eye. For example, one study[2] reported that, benzalkonium chloride (BAK), a preservative commonly used in eyedrops, has been associated with toxic effects such as "dry eye" and trabecular meshwork degeneration.

In response, European regulators now require special labelling for ophthalmic medications. Demand for PF medications is also driven by patients, who increasingly prefer natural, organic and PF products. Outside of Europe, preserved ophthalmic medications comprise the majority of the global market and are primarily delivered in small, multidose squeeze bottles.

In the US and beyond, a large portion of the global PF market currently uses single- or unit-dose packaging, which not only tends to be more expensive than bottles and overfilled for a single dose, but also difficult to use. PF multidose systems are a substantial improvement over these unit-dose packs.

> "For most patients, standard eyedroppers pose a challenge. Who among us hasn't missed their eye when trying to use one? Or who hasn't wondered whether the appropriate amount of medicine actually reached their eye?"

**Thomas Grinnan**
Vice-President,
Sales & Marketing, Healthcare
T: +1 804 923 1494
E: thomas.grinnan@SilganDispensing.com

**Ralf Hergenröther**
Product Line Manager,
Healthcare Solutions
T: +33 6 48 07 46 09
E: ralf.hergenroether@SilganDispensing.com

**Silgan Dispensing Systems**
Le Campus
6 rue Jean-Pierre Timbaud
78180 Montigny le Bretonneux
France

**www.silgandispensing.com**

## PATIENT NEEDS

Silgan Dispensing has built a reputation for expertise in PF dispensing and scaled manufacturing, as well as in-depth consumer insights and market research, enabling it to deliver innovative and customisable solutions to meet the needs of its clients. As a leading global supplier of highly engineered triggers, pumps, sprays and dispensing closure solutions, Silgan Dispensing products are seen every day in the home, health and beauty markets.

Silgan Dispensing's market research into the ophthalmic market revealed several trends: rising consumer preferences for natural, organic or PF products; the need for a more patient-friendly, PF, multidose packaging solution; and the global shift away from preservatives in ophthalmic medicines, particularly for chronic medications.

For most patients, standard eyedroppers also pose a challenge. Who among us hasn't missed their eye when trying to use one? Or who hasn't wondered whether the appropriate amount of medicine actually reached their eye? Using its market insight capabilities, Silgan Dispensing discovered that patients also want control, both in the amount of product dispensed and how it gets into their eyes. They want precision, so that they can be sure of how much product they are dispensing, and they want the ability to dispense only one drop at a time.

Figure 1: Iridya™ is Silgan Dispensing Systems' new preservative-free multidose eyedropper.

This need for precision was also confirmed by ophthalmologists, who requested more exact dosing for key diseases, such as glaucoma. Patients are also concerned with wasting medicine because of inadvertent overdosing due to dripping, jetting or streaming. And they want simple delivery to ensure the product actually makes it into their eyes.

> "A key attribute of Iridya™ is its strong anti-microbiological integrity, which was tested and proved by an independent laboratory."

## THE DEVELOPMENT OF IRIDYA™

Silgan Dispensing coupled its market insights, engineering and design, and industry experience to create a ground-breaking solution that answers both the dosing concerns of ophthalmologists and the control desired by patients – Iridya™ (Figure 1).

Silgan Dispensing began the product development process by discussing unmet needs with ophthalmologists, learning that existing PF solutions were not meeting patient needs for best-in-class medical care. The company assembled engineering and design teams to develop initial designs and prototypes. Development teams also studied how to create a product that would be resilient and secure from microbial access, taking the unmet market needs into consideration. In this process, Silgan Dispensing was able to leverage its extensive expertise in designing, manufacturing and scaling medical devices for filling at high speed on customers' filling lines while ensuring antimicrobial integrity, utilising more than a decade of PF nasal device experience.

Silgan Dispensing then benchmarked the design against competitor devices on the market and tested its system in consumer focus groups. Both competitor benchmarking and consumer research confirmed that it was on the right track and provided valuable feedback to improve the design to address more unmet patient needs. The final result is the Iridya™ system, launched at CPhI Worldwide in Madrid in October 2018.

## THE UNIQUE FEATURES OF IRIDYA™

Iridya™ is an eyedropper that improves on existing technology by combining advanced ergonomics and precise dispensing to ensure proper dosage, drop after drop. The device, which works for many formulations, provides an innovative solution for pharmaceutical partners, which may drive patient use and physician prescriptions.

### Ergonomics and drop control

Iridya™ features a familiar, round, squeeze bottle design, but what makes it unique to the PF market is its elongated tip, which ensures greater accuracy when administering drops to the eye. Adding to the convenience for patients are the low actuation force and ergonomic grip on the overcap – features that are often important to older patients (Figures 2 and 3). Overall, the eyedropper's balanced system is easier to handle and

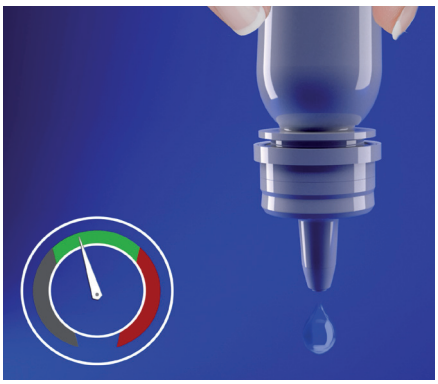

Figure 2: Iridya™ has a low actuation force.

Figure 3: The ergonomic grip on the overcap makes it easier for older patients to use.

provides patients with greater control when applying their drops.

Key factors in drop control are the device's Advanced Flow Control and NO-JET™ technologies. The Advanced Flow Control system ensures exceptional drop control for precise dosing down to the drop. The NO-JET™ technology helps to eliminate streaming or jetting, ensuring single doses drop after drop, even if the bottle is squeezed hard, throughout the life of the product.

### Safety and Flexibility

A key attribute of Iridya™ is its strong anti-microbiological integrity, which was tested and proved by an independent laboratory. Formulations are protected from contamination by a novel barrier system at the tip and other mechanical features within the device, including a sterile air filter, air filter protection and a shut-off valve. These innovative features provide maximum protection, and the materials used are compliant with existing ophthalmic regulations. The system is sterilised via gamma irradiation, has no metal contact with fluid and does not use silver ions (Figure 4).

Because of the device's Advanced Flow Control, Iridya™ adapts to different formulation properties, and its standard configuration is compatible with a range of low- to high-viscosity formulations. It also meets new formulation trends like gels or combination formulations and, because one standard model fits a wide range of formulations, Iridya™ can save supply chain and administrative costs.

Lastly, due to its round, standard bottle shape and shallow design, Iridya™ is compatible with most sterile multidose eyedropper filling lines. The snap-on closure design and large bottle neck allow for fast, easy filling. Silgan Dispensing Systems is working with multiple filling sites and machine manufacturers to supply Iridya™ for automated filling of ophthalmic formulations.

## HOW THE PF MULTIDOSE SYSTEM WORKS

Iridya™ works very much like a standard eyedropper squeeze bottle. When holding the bottle upside down, the user squeezes with thumb and finger. With this pressure, the formulation is pushed towards the outlet valve below the tip's orifice. Increasing pressure also compresses the spring-loaded

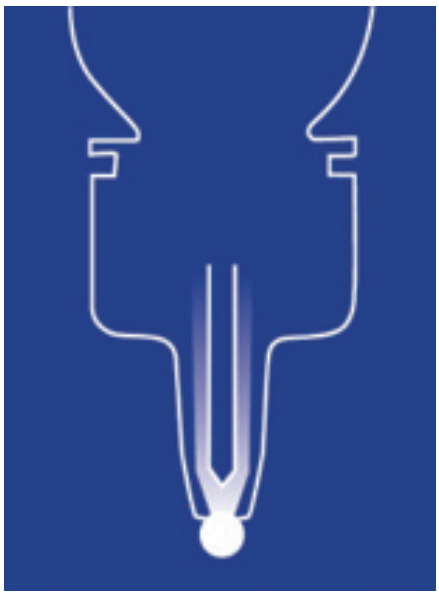

Figure 4: The innovative triple-barrier system inside the dropper provides strong microbiological safety and offers maximum protection of the formulation.

valve, allowing the formulation to flow. The valve closes immediately afterwards, as the squeeze force decreases, returning to its protected state. As liquid is forced out of the hermetically sealed system, air is also entering through the sterile air filter and back into the system for bottle venting. This innovative triple sealing and filtering technology prevents the liquid from flowing back into the system to keep the formulation contamination-free.

> "Users preferred the overall ergonomic feel and squeeze bottle familiarity of Iridya™ compared with all the solutions tested."

## CONSUMER TESTING

During the development of Iridya™, the Silgan Dispensing team conducted consumer focus group testing to gauge the effectiveness of its design at addressing consumer needs, and how the design compared to the performance of other PF droppers on the market (Figure 5).

In Europe and America, the Silgan Dispensing team performed multiple consumer focus group studies,[3] with each session featuring the following elements:

- General discussion.
- Tactile testing, where participants provided feedback relative to the packaging as they physically examined and opened it.
- Experiential testing, where participants dispensed drops into their eyes using Iridya™ and gave feedback on control, aiming, force to actuate and ergonomics.

The results of the consumer testing showed that participants favoured Iridya™, with it outperforming other available PF eyedroppers in aiming control and ease, one drop control and force to actuate. Additionally, Iridya™ was the only dropper that did not jet or stream when squeezed with force and there was no panelling or warping of the bottle. Users preferred the

Figure 5: The bottles are designed with consumers in mind, with both white and transparent options available and using soft material and coloured overcaps.

overall ergonomic feel and squeeze bottle familiarity of Iridya™ compared with all the solutions tested.

## CONCLUSION

Rising demand for patient-friendly PF eyedroppers drove the development of Iridya™. Consumer and market research were critical inputs to Silgan Dispensing's design and innovation process. Patients are looking for control – over both accurate dosing and how much product is dispensed. They want a device that helps them target the eye correctly, delivering an accurate dose, one drop after one drop, without wasted product. Physicians want an easy-to-use device with precise dosing and anti-microbial integrity.

Iridya™, Silgan Dispensing's new PF multidose eyedropper, solves the unmet needs of patients and the medical community by ensuring exceptional drop control and precise dosing for preservative-free medications, delivering a better patient experience and improved patient care. This new solution also affords pharmaceutical brands a new option that is compatible with most market formulations and has a validated sterilisation supply chain for device and bottle, making Iridya™ the ideal delivery system for both over-the-counter and prescription ophthalmic drugs.

## ABOUT THE COMPANY

Silgan Dispensing is a leading global supplier of highly engineered drug delivery devices to major pharmaceutical companies in the healthcare market. With its breadth and depth of technology, consumer insights and manufacturing expertise, Silgan Dispensing provides innovative and customisable solutions that meet brand owners' needs. At the same time, it makes sure patients can easily and reliably dispense the right dose. Its meticulous approach to pharmaceutical dispensing enables it to give both brands and patients better results.

Silgan Dispensing believes that every dispenser should have its own DNA – the unique elements that make it function flawlessly with the medication inside it and the patient who is using it. Silgan Dispensing's state-of-the-art dispensing solutions can be customised down to the smallest component, ensuring a safe, effective and easy dosing experience.

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## ABOUT THE AUTHORS


**Thomas Grinnan**, Vice-President, Sales & Marketing, Healthcare, Silgan Dispensing Systems, has worked in the pharmaceutical industry for more than 28 years as an executive, innovator, consultant and business development specialist. A biologist, he began his career in strategic consulting, working closely with pharmaceutical and medical device companies. After a long career at Westvaco, MeadWestvaco and Westrock's Healthcare and Patient Adherence packaging divisions, Mr Grinnan joined Silgan Dispensing Systems, a spin-off specialising in liquid dispensing solutions for nasal, topical and ophthalmic delivery. He received his BA from the University of Virginia (Charlottesville, VA, US) and his MBA from the University of North Carolina, Chapel Hill (NC, US).

**Ralf Hergenröther**, Product Line Manager for Silgan Dispensing Systems since 2007 has held various R&D, sales and marketing positions. As Global Marketing Lead in Healthcare Solutions, he actively promotes a large portfolio of dispensing products to pharmaceutical customers for nasal, ophthalmic, topical and otic applications. His main focus is to understand patient needs, regulatory concerns and packaging requirements, and to develop and market dispensing solutions that create a better experience for patients and doctors. Mr Hergenröther earned his MSc degree in engineering from FH Karlsruhe (Germany) and his business administration degree from HEC (France) in 2010.

# NEOPAC
## THE TUBE

# KEEPING PRESERVATIVE-FREE EYEDROPS STERILE WITH THE STERIDROP™ TUBE

**In this article, Ralf Künzi, Business Development Manager, New Products, Hoffmann Neopac, introduces the SteriDrop™ tube – a new multidose eyedrop delivery solution made in collaboration with Aptar Pharma. The SteriDrop™ tube offers strong barrier properties, simple manufacturing and increased ease-of-use for patients.**

The ophthalmic sector is becoming increasingly aware of the many side effects that can arise from sustained use of eyecare formulations containing ingredients such as benzalkonium chloride (BAC). The growing concerns surrounding such chemicals have brought about a comprehensive push for preservative-free eyecare solutions capable of combining sanitary eyedrop delivery with enduring efficacy.

Recently, Neopac, in collaboration with Aptar Pharma, introduced a solution that could revolutionise the manner in which eyedrops are dispensed while maintaining the product's effectiveness and safety – without the need for potentially harmful preservative chemicals (Figure 1). In addition to ensuring a preservative-free and sterile dispensing process, the new SteriDrop™ tube provides exceedingly high barrier protection, thanks to Neopac's proprietary Polyfoil® technology. Comprising a state-of-the-art multilayer structure with an integrated aluminum barrier, Polyfoil® yields exemplary protection against light, air, water vapour diffusion and substrate migration. It also supports critical content efficacy and overall product durability.

> "In addition to ensuring a preservative-free and sterile dispensing process, the new SteriDrop™ tube provides exceedingly high barrier protection, thanks to Neopac's proprietary Polyfoil® technology."


Figure 1: The SteriDrop™ tube.

However, the SteriDrop™ tube's key feature is optimally controlled dosing on a previously unattainable level. Crucially, SteriDrop™ tubes release a consistently sized drop only when pressure is exerted on the tube, thus preventing liquid from flowing back into the tube. This system effectively guarantees a level of

**Ralf Künzi**
Business Development Manager,
New Products
T: +41 31 770 11 11
E: ralf.kuenzi@neopac.com

**Hoffmann Neopac AG**
Burgdorfstrasse 22
3672 Oberdiessbach
Switzerland

**www.neopac.com**

microbiological safety, thus meeting the especially high demands for eyecare solutions. As a result, the product remains sterile over the entire period of application without the addition of potentially harmful preservatives.

This dispensing system, Aptar Pharma's Ophthalmic Squeeze Dispenser (OSD), has been microbiologically tested and FDA reviewed, which means the SteriDrop™ tube provides a pharma-grade solution that addresses the challenge of eyecare product protection and durability in products without preservatives (Figure 2). The metal-free fluid pathway for dispensing ensures suitability for sensitive formulations. A specially crafted tip seal mechanism closes the orifice immediately after a drop is dispensed, preventing contamination from external factors. This process helps eliminate the need for preservatives in the formulation, as well as additives such as silver ions in the surface coating.

SteriDrop™ tubes also provide added options for variety and marketability. With SteriDrop™, a broad range of tube sizes, up to 30 mL, offer a three-month dosage supply, while traditional bottles are typically available only in 5, 10 or 15 mL volumes. Furthermore, tubes generally offer enhanced branding opportunities via colour printing directly onto the tube body, rather than being limited by a label adhered to a bottle.

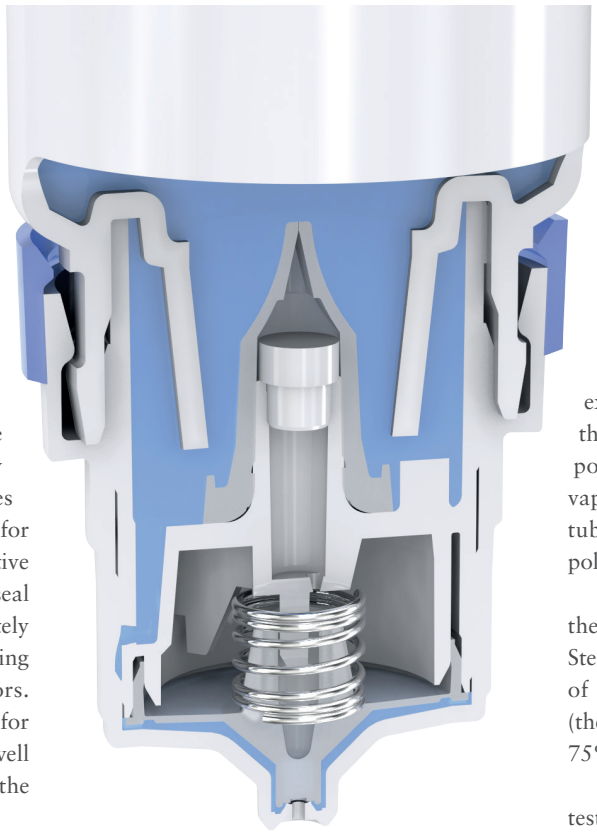

Figure 2: The SteriDrop™ tube's dispensing mechanism, Aptar Pharma's Ophthalmic Squeeze Dispenser.

## PROTECTION AND EFFICACY

SteriDrop™ tubes provide extra protection to eyedrop solutions as the container retains its shape until the last drop, due to the special coating of the Polyfoil® tube. To further protect against the tube head deforming upon application of pressure, SteriDrop™ tubes feature a specially engineered push-on interface with absolutely smooth interfacing surfaces, ensuring a tight, fully sterile connection between tube and applicator.

Additionally, the tubes have undergone an array of tests to ensure protection and integrity. First, SteriDrop™ has successfully passed the Tip Seal Integrity Test (TSIT) and Closure Ventilation Integrity Test (CVIT), both developed by Aptar and referenced for FDA approvals. Second, in studies regarding oxygen permeation, SteriDrop™ tubes experienced four times less permeation than in existing systems utilising standard polyethylene bottles. Similarly, water vapour permeation within the SteriDrop™ tubes was four times less than in polyethylene bottles.

These results (Figure 3) demonstrate the remarkable barrier capabilities of SteriDrop™ tubes, even under conditions of extreme temperature and humidity (these tests were performed in 40°C and 75% relative humidity).

Subjecting the tubes to such rigorous testing ensures their superior durability as well as proper maintenance of the tubes' contents. The SteriDrop™ solution is designed to reduce permeation, with the packaging's superior barrier properties protecting the enclosed product from environmental factors. The greater integrity of the barrier substantially differentiates SteriDrop™ tubes from competitors and minimises any loss in efficacy of product that may be caused, for example, by oxidation of sensitive active ingredients.

> "The tubes have undergone an array of tests to ensure protection and integrity. First, SteriDrop™ has successfully passed the Tip Seal Integrity Test and Closure Ventilation Integrity Test, both developed by Aptar and referenced for FDA approvals."

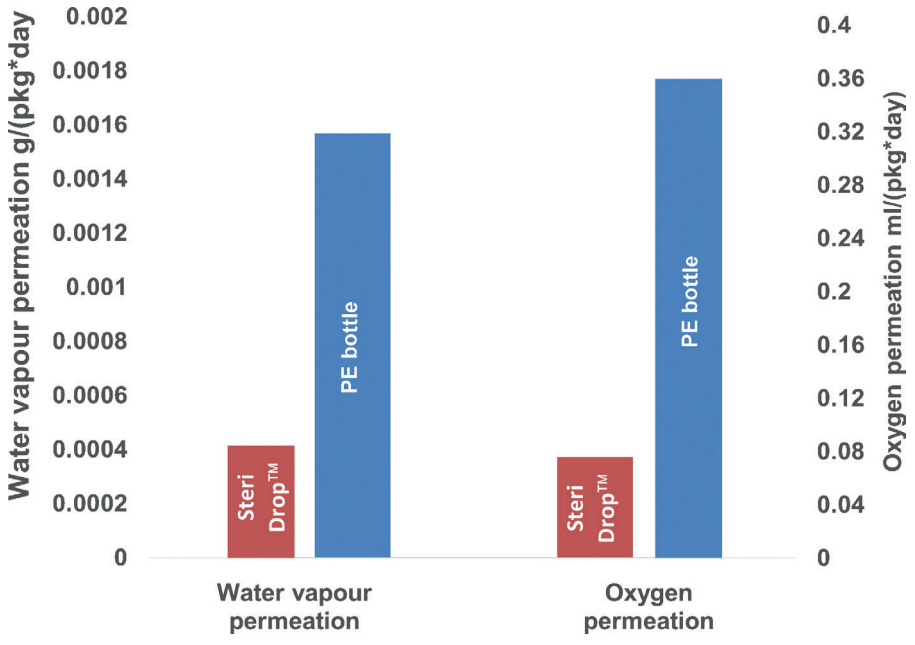


Figure 3: Water vapour and oxygen permeation results for polyethylene bottles and SteriDrop™ tubes.

> "The minimal packaging of the tube results in the discarding of significantly less plastic and product when compared to the vast majority of conventional unit-dose, blow-fill-seal systems."

## SUPPLY-CHAIN MANAGEMENT AND USER ACCESSIBILITY

The myriad benefits of the SteriDrop™ tubes don't end there, as simplicity of assembly for manufacturers and ease-of-use for patients are prioritised by design. From the onset of manufacturing, a concise supply-chain management process with a fully pre-assembled applicator tube allows for a highly efficient filling process. In other bottle manufacturing processes, two separate sterile components must be sourced and assembled, whereas, incorporating the SteriDrop™ tube requires just a single sourcing, filling and sealing step, with no need for additional labour or on-site sterile environment assembly.

Once implemented, the ergonomically advanced Polyfoil® tube not only elicits superior protection but provides a user-friendly experience for consumers, with the natural squeeze of the SteriDrop™ tubes facilitating easy handling and a simplified dispensing process for users. Polyfoil® technology also allows the drops to be dispensed predictably, precisely and with little pressure applied to the tube for ease of use and properly controlled dispensing. The result is not only a product that remains protected throughout its lifespan – even after initial package opening – but also ensures a consistent, concise user experience from the first application to the last.

## WASTE REDUCTION IN BOTH PRODUCT AND PACKAGING

Another notable perk of SteriDrop™ tubes is the drastic waste reduction compared with single-use systems. The minimal packaging of the tube results in the discarding of significantly less plastic and product when compared to the vast majority of conventional unit-dose, blow-fill-seal systems. Additionally, standard unit-dose containers contain more volume than required for a single application, leading to overfill and unnecessary waste.

With the SteriDrop™ tube, there is only a single, multidose package, which diminishes both cost and potential overfill. The tube size is custom-selected depending on the required dosing frequency to ensure patients receive the proper volume of product while reducing waste. And of course, utilising a single, multidose package that is reclosable while remaining sterile is decidedly more eco-conscious than discarding single-use packages en masse.

## CONCLUSION

Consumer demand for preservative-free eyecare solutions has spurred the development of the SteriDrop™ tube, complete with a user-friendly design and a strict dedication to safety and efficacy. The high barrier protection from the Polyfoil® technology works together with the tube's special dispensing unit to avoid contamination and safeguard the enclosed product from exposure.

Proven reduction in water vapour and oxygen permeation, even in the presence of extreme heat and humidity, certifies the durability of the SteriDrop™ tube as it protects its contents from environmental factors. With an emphasis on consumer ease, the tube is designed to ensure accessibility and safety for users. For manufacturers, a one-step sourcing and filling process allows for streamlined production.

As consumers' needs change, the industry must adapt accordingly and provide strategic solutions that prioritise safety without compromising efficacy. SteriDrop™ tubes successfully achieve such objectives in a rapidly evolving industry.

## ABOUT THE COMPANY

Hoffmann Neopac is a privately-owned company, headquartered in Thun, Switzerland. The company produces high-quality metal and plastic packaging in five locations: Hoffmann tins in Thun and CMP tins in Holland; Polyfoil® and plastic tubes with Neopac in Switzerland and in Hungary. Its longstanding customers include internationally active pharmaceutical, cosmetics and consumer goods manufacturers in the European and North American markets.

The company has recently taken a majority stake in 3D Technopack Ltd (Mumbai, India), thereby securing its foothold in the Asian market. With a new production facility in the US anticipated to be ready in Spring 2019, the company employs around a 1,000 employees and has a production capacity of 1.3 billion tubes.

## ABOUT THE AUTHOR

**Ralf Künzi** is Business Development Manager, New Products, for Hoffmann Neopac, where his responsibilities include finding new markets and applications for the company's high quality plastic packaging solutions. Neopac is especially known for its innovations in tube packaging.

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