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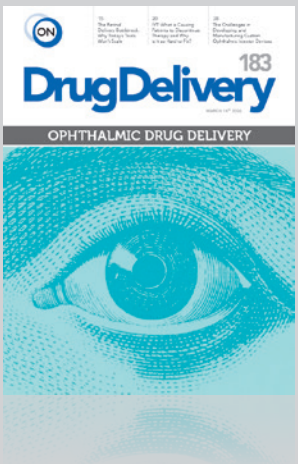
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OPHTHALMIC DRUG DELIVERY

ONdrugDelivery Issue N° 183, March 16th, 2026

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

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Current and Future Challenges:
Ophthalmic Drug Delivery Today and Tomorrow

In this issue of ONdrugDelivery, we put the spotlight on the ophthalmic sector. Ophthalmic delivery remains a highly challenging niche of drug delivery, defined by very low delivery volumes, delicate ophthalmic tissues, sensitive formulations and nervous patients. Specialists in this sector will be well-acquainted with these facets, and with novel biologic formulations and gene and cell therapies progressing through pharmaceutical pipelines, ophthalmic drug delivery is a potent target for innovation – a key subject in this issue.

Taking a broad view of the ophthalmic delivery landscape, **Sanner** considers the pressures and requirements of developing and manufacturing delivery devices across the various ophthalmic routes (Page 38). Then, focusing in on the topical route, **Nemera** discusses how increasing evidence of the side-effects caused by common preservatives has increased demand for preservative-free alternatives, such as its Novelia® multidrop preservative-free eyedroppers (Page 8).

Another key aspect of modern ophthalmology, intravitreal therapy, is a major theme throughout this issue. Contributing on this subject, **Bayer** and **SHL Medical** consider the challenges of treating retinopathy of prematurity, and describe how the two companies have collaborated on a novel solution to this problem (Page 24), while **West Pharmaceutical Services** discusses the advantages of using prefilled syringes in an ophthalmic context, along with the pros and cons of glass and polymer as materials (Page 30).

Looking towards the future of ophthalmic drug delivery, **TTP** considers how the sector's current approach to intravitreal therapy will face fundamental issues as demand increases, going on to advocate for a radical rethink of the tools and methods used to deliver these critical medications (Page 15). Further adding to this, **Fearsome** investigates the key issue of patients discontinuing their intravitreal treatments, presenting the burdens faced by these patients and a potential starting point for addressing them (Page 20).

Rounding out the issue, **WuXi AppTec** contributes a discussion on handling the ophthalmic side-effects of antibody-drug conjugates – a key modality in oncology – arguing that, with many of these drugs presenting high ocular toxicity, properly investigating the effects on the eye should be at the forefront of development for those operating in this sector (Page 46).

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NOVELIA®: ENGINEERING PRECISION, PROTECTION AND GLOBAL ADOPTION IN PRESERVATIVE-FREE MULTIDOSE EYE DROP DELIVERY

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we put patients first

Severine Duband and **Natalia Zabala** of **Nemera** discuss the role of multidose preservative-free eyedroppers in the ophthalmic market, highlighting the advantages of Nemera's Novelia® platform, including its non-return valve system, the sustainability of multidose delivery and the platform's growing success within the Chinese market.

ENGINEERING MICROBIOLOGICAL INTEGRITY IN PRESERVATIVE-FREE MULTIDOSE DELIVERY

Most ophthalmic eye drops still rely on preservatives to maintain sterility. Benzalkonium chloride, the most widely used preservative, has long been associated with ocular surface toxicity, particularly in chronic conditions such as glaucoma and dry eye disease.[1] As treatment durations increase and patients remain on therapy for longer periods, the tolerability of preserved formulations has come under growing scrutiny.

Advances in primary container closure systems have enabled the development of multidose preservative-free (MDPF) solutions designed to maintain sterility without chemical preservatives, while continuing to support ocular surface health and long-term treatment sustainability.[2] However, while more than half of currently available MDPF bottles rely on 0.22 µm sterile mesh filters to prevent microbial ingress and manage air compensation, research has questioned the robustness of filter-based systems under real-world conditions.[3] Because these filters are porous by design, they do not provide a continuous physical barrier, potentially introducing vulnerabilities during extended in-use periods and repeated patient handling.

Nemera's alternative approach is based on a non-return valve system combined with a dedicated silicone air-compensation membrane. The non-return valve ensures that no contaminated liquid can be

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reintroduced into the container after a drop has been dispensed, completely removing the need to filter the liquid pathway. Air intake occurs via a separate venting system that incorporates PureFlow® technology – a solid, homogenous silicone membrane. Unlike bacterial mesh filters, this material is non-porous and contains no holes, allowing its permeability characteristics to be precisely engineered while maintaining a continuous physical barrier against contamination.

An independent review of MDPF systems concluded that Novelia® provides "the largest amount of published information regarding the safety and sterility of these MDPF packages" and demonstrated resilience under both expected real-world microbial challenges and more severe stress scenarios.[4]

NOVELIA®: DESIGNING FOR DOSE PRECISION AND PATIENT CONTROL

In 2020, Nemera's R&D department, the Insight Innovation Centre, conducted a qualitative study involving patients and healthcare professionals to explore real-world administration challenges in dry eye and glaucoma therapies, in which interviews consistently revealed a perceived lack of control during eye drop administration. Both dry eye and glaucoma patients highlighted difficulty in reliably delivering a single drop as a primary frustration. Participants reported that multiple drops could be expelled unintentionally or that leakage could occur before actuation. These issues became increasingly pronounced towards the end of a product's life, when higher squeeze force was required and patients felt progressively less confident in controlling dose delivery.

While these challenges may represent inconvenience for some dry eye patients, they are more consequential for glaucoma patients, who may question whether the correct therapeutic dose has been administered and worry about costly medication being depleted prematurely. Correct instillation remains a significant barrier in chronic ophthalmology, with studies indicating that a substantial proportion of glaucoma patients struggle with proper administration technique.[1] Therefore, an intuitive, easy-to-use delivery

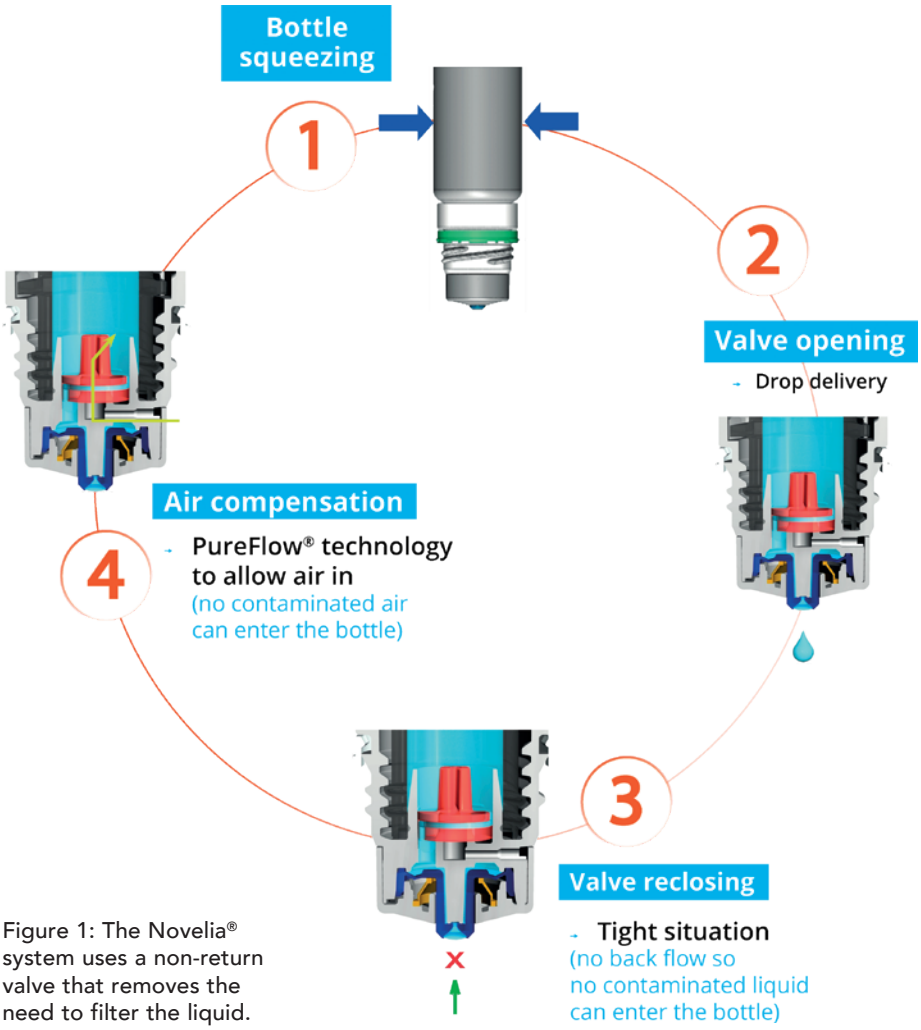


Figure 1: The Novelia® system uses a non-return valve that removes the need to filter the liquid.

system plays a critical role in supporting adherence, reinforcing patient confidence and ensuring long-term treatment continuity.

Novelia®'s PureFlow® technology not only functions as an air-compensation system but also as a controlled flow mechanism (Figure 1). The integrated design avoids uncontrolled multidrop delivery and supports the consistent release of a single calibrated drop at each actuation, regardless of bottle fill level.

To accommodate formulation diversity, Nemera offers three PureFlow® variants engineered for a wide viscosity range, from highly fluid to highly viscous solutions. In addition, five valve sizes are available, enabling precise adjustment of drop size according to product specifications and therapeutic requirements. This modular architecture allows pharmaceutical partners to tailor device performance to the needs of their formulations while enhancing patient confidence, reducing frustration and limiting unnecessary medication waste.

As ophthalmic pipelines increasingly incorporate higher-viscosity systems designed to improve ocular residence time and therapeutic efficacy, delivery platforms must maintain precision, microbiological integrity and usability across diverse

"CORRECT INSTILLATION REMAINS A SIGNIFICANT BARRIER IN CHRONIC OPHTHALMOLOGY, WITH STUDIES INDICATING THAT A SUBSTANTIAL PROPORTION OF GLAUCOMA PATIENTS STRUGGLE WITH PROPER ADMINISTRATION TECHNIQUE."

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formulation profiles. For Nemera, "We Put Patients First" is more than a corporate statement; it reflects a structured and systematic development philosophy. Integrating patient insights early in the design phase enables behavioural considerations to be incorporated into product specifications, risk management processes and user-focused failure mode and effects analysis. By embedding patient needs and practical constraints into formal quality frameworks, Nemera ensures that usability is addressed alongside microbiological safety and mechanical performance.

ERGONOMICS, ACTUATION FORCE AND REAL-WORLD USABILITY

Clinical studies have demonstrated statistically significant variability in the force required to expel a drop from commonly prescribed glaucoma medications.[5] Variations in actuation force influence patient confidence, dosing consistency and overall usability, particularly in elderly populations or in patients with reduced dexterity.

In 2015, Nemera commissioned independent user testing to assess comparative device performance and patient perception in real-world settings. Participants were selected based on demographic criteria (age and gender) as well as ophthalmic condition, including glaucoma and dry eye disease. Interviews were conducted in patients' homes in both the US and the UK to reflect actual usage environments. The study concluded that 76% of participants expressed a preference for Novelia® compared with other MDPF systems available at the time.

Key drivers of preference included the intuitiveness of the screw-on cap, the reassurance associated with tactile feedback and the stability of squeeze force throughout product life. Novelia® demonstrated only a 6% increase in required actuation force from the beginning to the end of treatment, compared with approximately 35% observed in alternative MDPF systems. Maintaining consistent squeeze performance is particularly important for patients with reduced dexterity, tremors or arthritis, who must be able to handle and manipulate the device reliably for each administration. One Amazon customer review for Systane™ Hydration PF (Figure 2) reads "I have arthritis in my hands and all the other brands are so hard to nearly not working at all to squeeze out even one drop. This dispenser works with gentle pressure every time. I am so glad to have found them."



Figure 2: Systane™ Hydration PF MDPF Lubricant Eye Drops for the treatment of dry eye launched in the US market with Novelia® (image courtesy of Alcon, Geneva, Switzerland).

"NOVELIA® DEMONSTRATED ONLY A 6% INCREASE IN REQUIRED ACTUATION FORCE FROM THE BEGINNING TO THE END OF TREATMENT, COMPARED WITH APPROXIMATELY 35% OBSERVED IN ALTERNATIVE MDPF SYSTEMS."



Figure 3: Commercial launch of Eyesucom® in China with the Novelia® MDPF platform.

In chronic ophthalmic conditions, usability is not a secondary consideration but a determinant of adherence. Variability in squeeze force, inconsistent drop formation or lack of intuitive handling can lead to dosing uncertainty and reduced persistence. By combining controlled flow architecture with ergonomic stability, Novelia® addresses both the mechanical and behavioural dimensions of eye drop administration.

GLOBAL VALIDATION: REGULATORY MILESTONES AND COMMERCIAL SCALABILITY

Novelia® has achieved significant regulatory and commercial milestones in China. The platform is listed on the Center for Drug Evaluation platform (Figure 3),[6] enabling referencing of Nemera's drug master file within drug product applications and facilitating regulatory integration in the Chinese market. Commercial validation has also been achieved through its integration into Eyesucom® (隐形眼镜润眼液) –

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Figure 4: A full range of bottles is available in LDPE, 5, 7.5, 11 and 15 mL.

a preservative-free lubricant eyedrop launched in partnership with Haohai Qisheng (Shanghai, China). Together, Eyesucom's regulatory publication and market adoption demonstrate the robustness and scalability of the Novelia® MDPF platform within one of the world's most tightly regulated ophthalmic environments.

Globally, Novelia® supports more than 550 prescription and over-the-counter (OTC) references across more than 55 countries spanning Europe, Latin America, North America, Oceania, the Middle East and Asia-Pacific. This broad footprint reflects sustained confidence in non-filter-based MDPF technology across both mature and emerging markets.

Novelia's scalability is further reinforced through its configurability and manufacturing flexibility. Novelia® is available in low-density polyethylene (LDPE) bottle formats of 5, 7.5, 11 and 15 mL (Figure 4), validated for both gamma and ethylene oxide sterilisation processes. Soft technology optimises squeeze force, while blow-fill-insert-seal technology through Nemera's partner Rommelag (Sulzbach-Laufen, Germany) expands compatibility with diverse formulation and regulatory requirements. Custom colour options enable brand differentiation and alternative cap technologies – including silver-ion and vented configurations – address specific formulation needs. Together with dual-continent manufacturing capabilities, these configurations position Novelia® as a scalable MDPF solution capable of supporting multinational product strategies from development through commercial launch.

DUAL-CONTINENT INDUSTRIAL FOOTPRINT: SCALABILITY AND SUPPLY RESILIENCE

To support growing global demand for MDPF systems, Nemera has further expanded its manufacturing capabilities in the US, effectively doubling production capacity for Novelia® multidose eyedroppers (Figure 5). This expansion strengthens the company's dual-continent manufacturing capabilities and reinforces supply resilience for global pharmaceutical partners. The new ISO 7 cleanroom facility spans more than 9,000 square feet and integrates high-speed assembly and injection-moulding capabilities, enhancing scalability while maintaining the stringent quality standards required for drug-device combination products.

In parallel, Nemera has expanded its capacity at its La Verpillière site in France through the addition of a new production line for Novelia® Standard and Novelia® Vent devices using identical core technology and components. The extension supports larger batch sizes and shorter lead times under established quality control processes. Collectively, these investments strengthen Nemera's industrial scalability while preserving the high standards expected for combination products.

SUSTAINABILITY IN MDPF: FROM FORMAT EFFICIENCY TO MATERIAL INNOVATION

Single-use unit doses raise concerns regarding cost, waste and convenience, particularly in chronic therapies.[4] Handling challenges among elderly patients may also increase contamination risk.[7] With the global glaucoma population projected to exceed 111 million by 2040,[8] practical and sustainable long-term delivery formats are becoming increasingly important.

Nemera conducted a comparative analysis evaluating Novelia® MDPF delivery against single-use unit-dose



Figure 5: New ISO 7 cleanroom extension at Nemera's La Verpillière facility in France, which enables doubled production capacity and reduced lead times.

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packaging for a typical glaucoma regimen (one drop per eye, twice daily) over one month. The multidose configuration used eight times less plastic, generated 25 times less drug waste and required nine times less transportation energy compared with the equivalent unit-dose format, highlighting the environmental advantages of MDPF systems across the treatment lifecycle.

Beyond format efficiency, sustainability also requires addressing material impact. Lifecycle assessment identified raw materials as a significant contributor to a product's carbon footprint. In response, Nemera developed a bio-based resin version of Novelia®, derived from second-generation crude tall oil residues. This alternative reduces Novelia's carbon footprint while maintaining identical device design, performance and pharmaceutical-grade compliance. Extractables testing confirmed regulatory compatibility, enabling adoption of the bio-resin configuration without altering device functionality or quality standards.

Nemera's broader sustainability strategy aligns carbon reduction, responsible sourcing and eco-design objectives, supported by EcoVadis Gold status (top 5% globally) and Science Based Targets initiative commitments across operations and supply chain.

INTEGRATED COMBINATION PRODUCT SUPPORT

Nemera provides laboratory services including in-use simulation over two weeks, drop size analysis (variable depending on valve size), flow control and squeeze-force evaluation to determine the optimal Novelia® configuration for each formulation. Based on performance data, Nemera's team recommends the appropriate PureFlow® control, bottle type, valve size and cap technology aligned with therapeutic requirements.

These programmes may also include microbiological challenge testing on the combination product, as well as functional assessment under extreme storage conditions, including temperature cycling and stress scenarios. The outcome is submission-ready documentation designed to support global regulatory filings and de-risk development timelines.

"THROUGH A NETWORK OF FORMULATION LICENSORS, FILLING PARTNERS AND INDUSTRIAL COLLABORATORS, NEMERA SUPPORTS THE DEVELOPMENT OF FULLY INTEGRATED DRUG-DEVICE COMBINATION PRODUCTS, ACCELERATING TIME TO MARKET WHILE MAINTAINING COMPLIANCE WITH REGIONAL REGULATORY FRAMEWORKS."

Nemera's regulatory experts support customers throughout the submission process, providing guidance on required documentation, technical files and supportive data packages for registration. In addition, Nemera can facilitate access to ready-to-use dossiers for selected molecules suitable for private labelling in combination with the Novelia® delivery system. Through a network of formulation licensors, filling partners and industrial collaborators, Nemera supports the development of fully integrated drug-device combination products, accelerating time to market while maintaining compliance with regional regulatory frameworks.

While device ergonomics play a central role in usability, patient education remains equally important in mitigating unintentional non-compliance.[9] Educational resources supporting correct eye drop administration improve technique and adherence. Nemera therefore extends its support beyond device supply, assisting customers during product launch through dedicated training for sales teams and healthcare professionals, as well as materials to support promotional and educational initiatives. Customisable patient guidance videos, available in multiple languages, further reinforce correct usage and adherence across global markets.

THE FUTURE OF MDPF: PERFORMANCE, SUSTAINABILITY AND SCALE

Over the next three to five years, MDPF systems are expected to become standard across both prescription and over-the-counter ophthalmics, driven by long-term ocular surface protection, patient convenience and sustainability. At the same time, formulation innovation is progressing towards higher-viscosity systems and advanced therapeutic approaches, placing greater demands on delivery precision, microbiological integrity and device-formulation compatibility.

In this evolving landscape, MDPF platforms must combine configurability, regulatory robustness, industrial scalability and environmental responsibility. Through continued investment in technology, sustainable materials and global manufacturing capacity, Nemera aims to support the next generation of safe, effective and patient-centric ophthalmic therapies.

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Severine Duband is Strategy & Marketing Director for the Ophthalmics and Nasal Business Unit at Nemera, where she drives the overall business unit strategy for Nemera's proprietary drug delivery devices. Her responsibilities include managing the product portfolio and leading innovation initiatives, as well as driving strategic partnerships with a strong focus on ear-nose-throat, dermal and ophthalmic routes of administration. A graduate of EM Lyon Business School (France), Ms Duband began her career in the fast-moving consumer goods sector, where she spent a decade overseeing strategic planning, new product launches, project management and brand communication. In 2018, she joined Nemera's Global Marketing team as Global Category Manager, specialising in the parenteral segment. She later advanced to lead the Marketing department for drug delivery devices in 2022, before taking on her current role as Strategy & Marketing Director.

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Natalia Zabala has been Global Marketing Category Manager for Nemera's ophthalmic franchise since September 2025, leading the global strategy for Novelia®, Nemera's flagship multidose preservative-free platform. With extensive international marketing experience, she focuses on aligning innovation with pharmaceutical partner needs and evolving patient expectations.

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THE RETINAL DELIVERY BOTTLENECK: WHY TODAY'S TOOLS WON'T SCALE

Dr David Cottenden and **Benjamin Hatton** of **TTP** examine the rapid shift towards cell and gene therapies in ophthalmology, indicated by current pharmaceutical pipelines, and reveal a potential delivery crisis – today's surgical capacity cannot support what the pipeline demands. Considering this, they explore why a radical rethink of retinal delivery tools could unlock scalable access to the retina.

DRUG DELIVERY TO THE EYE IS CHANGING

The pharmaceutical industry is always in flux, which is the mark of a healthy technology sector. Ophthalmic drugs are no exception – where the landscape was dominated by small molecules 20 years ago, the last 10 to 15 years have seen the rise of biologics and an increasing focus on diseases of the back of the eye. This has, in turn, driven a revolution in workflows to enable an ever-growing number of intravitreal injections to be administered with an astonishing safety and efficacy profile.

Given that changes over the last 10 years have been profound, what will drug delivery to the eye look like in ten years from now? TTP's analysis of public data

> "TTP'S ANALYSIS OF PUBLIC DATA ON DRUGS FOR THE EYE PLANNED FOR LAUNCH IN THE US OR EUROPE GIVES AN UNUSUALLY CLEAR ANSWER – THE TREND IN 2035 WILL BE TOWARDS STRONG GROWTH IN CELL AND GENE THERAPIES TARGETING HIGH-PREVALENCE DISEASES OF THE RETINA."

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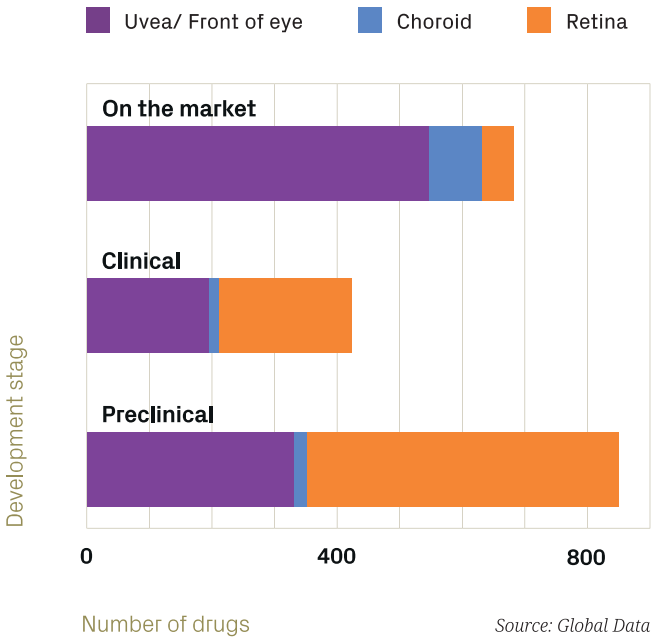


Figure 1: Ophthalmic drugs by target site and development stage.

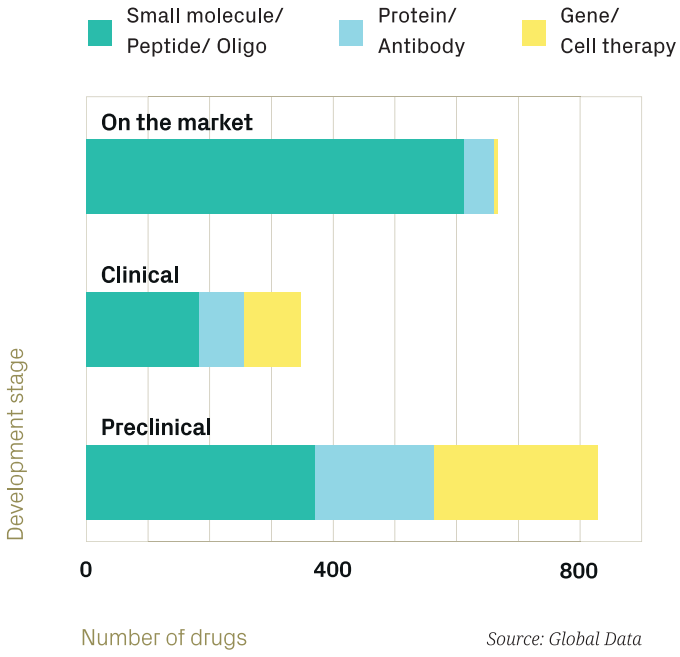


Figure 2: Ophthalmic drugs by drug class and development stage.

on drugs for the eye planned for launch in the US or Europe (Figures 1 and 2) gives an unusually clear answer – the trend in 2035 will be towards strong growth in cell and gene therapies targeting high-prevalence diseases of the retina.

Even though many of the drugs in pipelines – especially those in preclinical stages – will not progress to become marketed therapies, drop-out in the drug discovery process is unlikely to change this basic conclusion. Looking first at the target site (Figure 1), while only about 10% of currently marketed therapies target the retina, more than half of the current preclinical assets do. A large majority of the 500 preclinical assets that target the retina will never reach the market, but drugs targeting the retina will represent a much larger proportion of the market than they do today.

Considering the class of therapy (Figure 2), the story is very similar. Currently marketed therapies are mostly small molecules by number (though biologics are more significant by value and, arguably, by impact), whereas they are a minority in the preclinical pipeline, with cell and gene therapies approaching a third of the considered preclinical assets (amounting to more than 250 assets). The trend is clear and robust – so, when these pipeline assets come to fruition, what might the implications for drug delivery be?

IS DELIVERY READY FOR THESE NEW DRUGS?

At present, drug delivery to the eye is dominated by topical eye drops and intravitreal liquid injections. Eye drops are mostly self-administered and provide an effective (although weakly-targeted) method to deliver small molecules to the front of the eye. Intravitreal therapies (IVTs) are administered by healthcare professionals, mostly in non-surgical settings, delivering both small molecules and biologics to the back of the eye. It has been estimated that around 15 million intravitreal injections were performed in the US in 2024.

Can either of these techniques serve the upcoming need to deliver cell and gene therapies to the retina for high-prevalence diseases such as age-related macular degeneration (AMD), diabetic macular oedema (DME) and geographic atrophy (GA)? The answer to this is primarily driven by anatomy – the question is in identifying the structures that exist in the eye between the retina and the delivery site that might limit the spread of cells or gene vectors.

There are essentially two ways into the retina – through the front via the vitreous humour and through the back via the choroid (Figure 3), both of which are regulated by selectively permeable membranes. Bruch's membrane

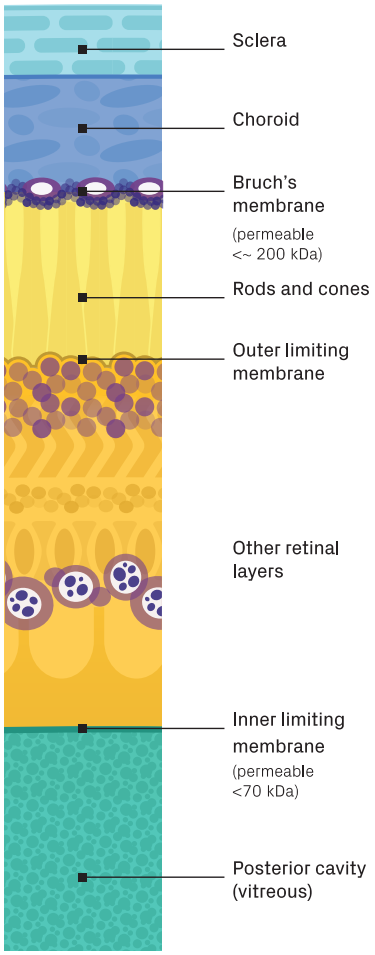


Figure 3: Posterior section of the eye showing sclera, choroid and retinal layers (layer thicknesses are not to scale).

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controls entry via the choroid, only allowing in molecules under approximately 200 kDa (closer to 100 kDa for older patients); whereas the inner limiting membrane controls entry via the vitreous humour, restricting the ability of molecules above approximately 70 kDa to access the retina.

For comparison, a gene therapy with an adeno-associated virus vector is about 5 MDa, and therapeutic cells are, of course, far bigger. Even without considering the effects of outflows from the eye and degradation, it is clear that – exceptional circumstances aside – if cell or gene therapies are delivered outside of the retina, they will stay outside of it.

That said, exceptional circumstances do occur. For example, a cell therapy may treat the retina by introducing cells into the vitreous humour that then manufacture a therapeutic that is small enough to pass into the retina. Furthermore, neither membrane is as simple as a sieve, so slightly larger molecules with appropriate chemical properties will be able to penetrate to some extent. However, the difference in size between the membranes' "cut-offs" and even a small gene therapy is very large, so delivery outside the retina will often be insufficient.

So, if eye drops and IVTs will not be able to deliver many of the next generation of retinal therapies, what about other existing techniques? There are existing methods for delivering therapies subretinally, of which the more established methods involve accessing the retina from the front via ports in the anterior sclera, typically post-vitrectomy. Another approach (presently still undergoing trials) involves threading a cannula through an incision in the sclera, through the suprachoroidal space and then extending a fine needle into the retina from behind.

Both techniques have a number of limitations. The rate of complications (>50%) and serious adverse events (>1%) is relatively high compared with IVT and, as surgical procedures, they are far more time-consuming (one to two hours versus around 15 minutes) and expensive (over US$10,000 (£7,400) versus around $600).

However, the biggest limitation by far is availability. There are presently fewer than 20 centres in the US that can deliver these subretinal procedures. But, even if the entire surgical capacity of US retinal specialists were redirected solely to subretinal drug delivery, it would still only enable around 1,500,000 treatments per year. With more realistic constraints, 150,000 treatments per year might be achievable. Even if the dosing regimen for newer drugs were to reduce the number of procedures needed significantly, this is not a near-miss – the capacity of the healthcare system to deliver subretinal drugs is only a fraction of what is needed. Drug delivery to the retina needs a revolution.

"EVEN IF THE DOSING REGIMEN FOR NEWER DRUGS WERE TO REDUCE THE NUMBER OF PROCEDURES NEEDED SIGNIFICANTLY, THIS IS NOT A NEAR-MISS – THE CAPACITY OF THE HEALTHCARE SYSTEM TO DELIVER SUBRETINAL DRUGS IS ONLY A FRACTION OF WHAT IS NEEDED."

HOW MUST DELIVERY DEVICES ADAPT FOR ADVANCED OCULAR THERAPIES?

Having said retinal drug delivery needs a revolution, it is a short step to the need for radically improved delivery tools. The reason is simple – the only way to deal with the essential problem of surgical bandwidth is to reduce the complexity and invasiveness of the delivery procedure to the point where it takes far less time, does not require the same limiting level of skill and, ideally, ceases to be considered a true surgical procedure, much as has already happened with IVT. This level of procedural simplification can be enabled by a complete rethinking of the delivery tools.

So, what does a radically improved delivery tool look like? A lot remains to be determined, but the following key points are likely requirements:

- **Direct Delivery to the Retina:** This almost certainly means introducing a very fine needle (often 48G) into the retina, probably at an acute angle to the surface to avoid issues with the bevel length.
- **Less Invasive:** This could mean avoiding the need for vitrectomy and multiple ports in the sclera. The "subretinal-via-the-suprachoroidal-space" approach currently in trials has gone some way towards this.
- **Compatible with Cell and Gene Therapies:** Amongst other things, this means that the system (perhaps including accessories) must be closed, so as to avoid viral contamination of the environment, and must offer low-shear fluidics to avoid damage to cells.
- **De-Skill the Procedure:** This is a high bar – and one that varies by territory – but the essence of it is achieving very low infection risk, very low complication rate and a procedure that is both quick and simple.

These requirements are a significant challenge – so is there any reason to think that they might be achievable? For now, a way to consider this is to look at the development of procedures in other areas of surgery. Aortic valve replacement is a good comparison, involving detailed structure, difficult access and high criticality. The evolution of early open-heart procedures, taking five hours with a full sternotomy and cardiopulmonary bypass, into current transcatheter procedures, taking as little as 45 minutes and an incision of less than a centimetre, gives some insight into what might be achievable for retinal delivery.

The example of aortic valve replacement suggests the need to think hard about the following points:

- **Access Routes:** Identifying a means of accessing the target site by a minor incision in a much less sensitive location, thereby avoiding more traumatic direct access, is key. The exploration of accessing the retina via the suprachoroidal space is promising in this regard, though the challenge of choroidal haemorrhage suggests that there is more still to achieve.

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- **Effective Imaging:** Indirect access always makes visualisation harder, so a combination of imaging techniques will be needed both to guide the clinician to the site and to enable a successful procedure to be performed once it is reached. Ophthalmology is quite well-equipped with imaging approaches, which is a great advantage.
- **Robust Stabilisation:** "Anchoring" the tools to a solid reference point close to the procedure site is vital for enabling precision and avoiding "jitter". A good mounting point needs to be solidly connected with the target.



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"THE CHALLENGES OF RETINAL DRUG DELIVERY ARE SUBSTANTIAL, BUT THERE IS EVERY REASON TO THINK THAT THEY CAN BE MET."

Aortic valve replacement is not a unique example of such profound developments in technique and tooling. While the challenges of retinal drug delivery are substantial, there is every reason to think that they can be met.

IS THERE TIME TO BRIDGE THE GAP?

Pharma pipelines look around ten years into the future – how does that compare with the time that a revolutionary procedure and device will take to come to fruition? Data from TTP's own extensive product development show that developing a drug delivery device, from a clear vision and a clean sheet through to verification testing, takes four to five years, with scaling and regulatory work fitting around that timescale. However, in this case, where transforming the procedure and creating the product are so interconnected, the device vision is not – and cannot yet be – clear.

In situations like this, it almost never makes sense to begin developing a commercial product straight away, as it will either be too flexible to be economical or easy to use, or be built on assumptions that cannot possibly be evidenced at this stage. Instead, the better approach is usually to create tools to learn with – focused devices that can be used to test approaches and assumptions about core procedures and product direction, including clinician needs and preferences, testing on animal eyes *ex vivo*, *in vivo* animal testing, cadaver work and perhaps first-in-human trials.

These tools are designed for ease of iteration and flexibility, not cost and manufacturability; for function and handling, not appearance. They are not an "early prototype" of an eventual product – they are a key means by which the product can be defined. How long this process takes is very context-dependent, but it is usually several years. Comparing these activities to typical pipeline timescales, there is still time to think big and revolutionise drug delivery to the retina – but there is little time to spare.

"COMPARING THESE ACTIVITIES TO TYPICAL PIPELINE TIMESCALES, THERE IS STILL TIME TO THINK BIG AND REVOLUTIONISE DRUG DELIVERY TO THE RETINA – BUT THERE IS LITTLE TIME TO SPARE."

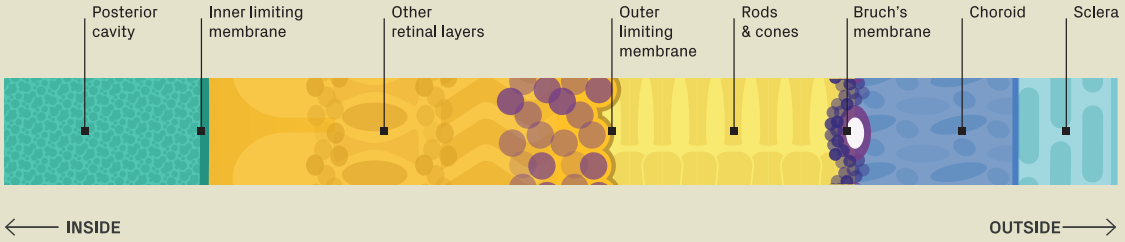
WHERE CONTENT MEETS INTELLIGENCE ONdrugDELIVERY

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Drug delivery to the eye

Anatomy, drugs, and approaches

Ocular drug delivery is rapidly evolving, driven by new drugs and emerging therapeutic classes. The focus is shifting toward the back of the eye and increasingly large molecules, stretching the limits of existing delivery approaches. This sheet is designed to support development engineers navigating these new demands, highlighting key challenges, exploring delivery options, and helping identify viable pathways quickly.



Cross-section of the base of the eye showing sclera, choroid, and retinal layers; layer thickness not to scale

		Small molecules	Proteins	Fusion proteins	Monoclonal antibodies	mRNA	Gene therapies	Cell therapies
Mass of therapeutic		100-1000Da	5-70kDa	50-150kDa	~150kDa	1-2MDa	1-5MDa	>1GDa
Description		Low molecular weight organic compounds; often inhibit enzymes or receptors; penetrate tissues easily	Polypeptides or proteins; act as enzymes, inhibitors, or signalling molecules	Engineered proteins combining functional domains (e.g. receptor fused to antibody fragment)	Large antibodies; highly specific binding to target antigens (e.g. VEGF)	Messenger RNA encoding proteins; induces cells to produce therapeutic proteins	Vectors delivering genetic material for long-term protein expression or gene editing	Live cells administered to replace/repair damaged tissue or modulate immune responses
Target location	**Uvea**	■ ■ ■	□ ■	■	■	■	■	■
	Choroid	■ ■ ■	■ ■ ■	□ ■ ■	■	■	■	■
	Retina	■ ■ ■	■ ■ ■	□ ■ ■	■ ■	■	■	■

About the table

The coloured squares show which delivery approaches can get each drug type to each target location; for example, proteins can be delivered to the retina suprachoroidally (■), intravitreally (■), or subretinally (■). □ shows partial delivery.

Topical

Liquid delivery to the cornea; highly mature; preservative-free devices are newer but growing.

Intravitreal

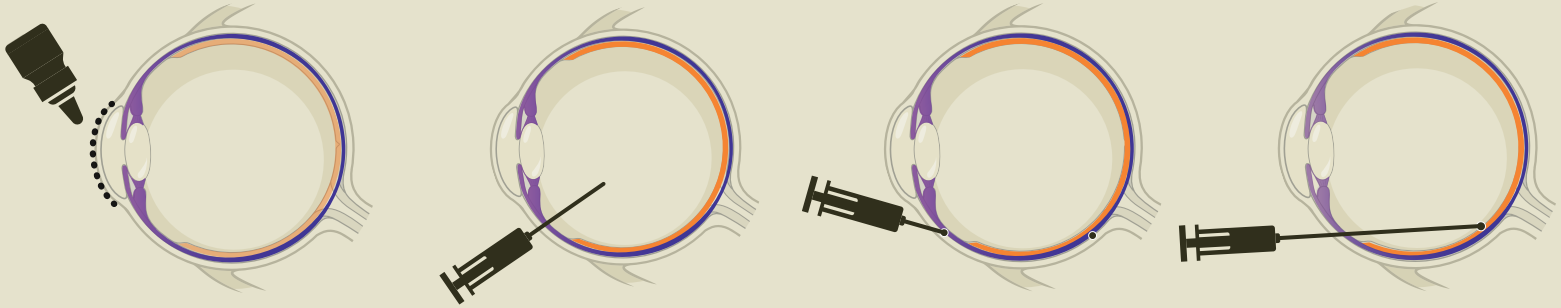
Both PFS and vial-and-syringe based systems are highly mature and efficient; proprietary solid delivery devices also exist.

Suprachoroidal

Exploratory devices for delivery to the front or back of the suprachoroidal space exist; market maturity is low.

Subretinal

Surgical tools - often building on existing vitrectomy towers - are the state of the art.



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Expert View

INTRAVITREAL INJECTIONS – WHAT IS CAUSING PATIENTS TO DISCONTINUE THERAPY AND WHY IS IT SO HARD TO FIX?

Gregg Draudt of Fearsome considers the significant issue of treatment discontinuation in intravitreal therapies, digging into the root causes of poor adherence and what will be required to reverse this trend in a way that caters to the full range of stakeholders, who often have contradictory requirements.

If you have attended a recent ophthalmology conference or looked at the academic literature, you will have heard that the issues of patient burden and non-adherence associated with intravitreal injection therapy (IVT) are currently a major point of concern. The estimate is that as many as 50% of patients stop their therapy within four years. Investigating the influential factors that cause people to discontinue treatment, this article provides a system-level view of IVT, highlighting how misaligned stakeholder priorities can make things harder for patients.

HOW DID WE GET HERE?

In the mid-2000s, the landmark approvals of anti-vascular endothelial growth factor (anti-VEGF) drugs – especially Lucentis (ranibizumab, Genentech) – revolutionised treatment for neovascular diseases such as wet age-related macular degeneration, diabetic macular oedema and retinal vein occlusion. Over the following 15 years, anti-VEGF use exploded to millions of injections per year.

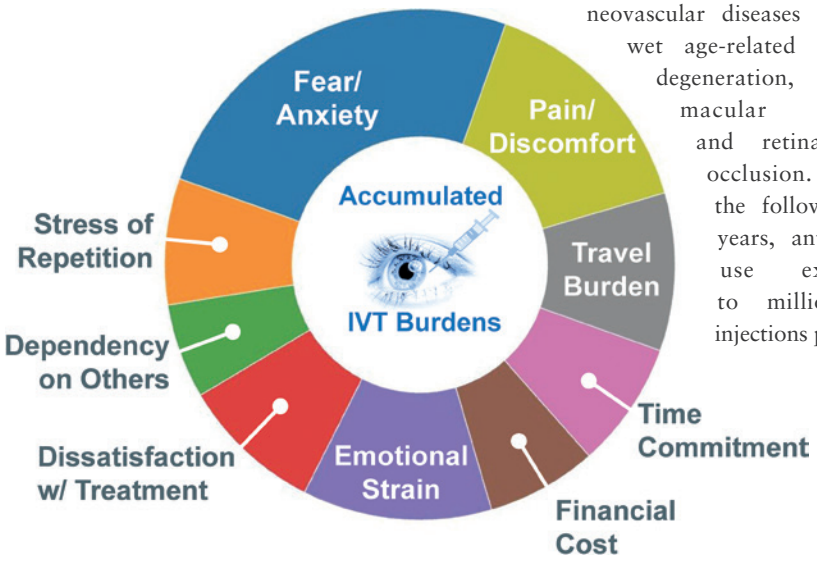


Figure 1: Accumulated burdens (side-effects play a significant role in these burden groupings).

While being hailed as an amazing therapy, anti-VEGF patients require an anxiety-laden monthly dosing regimen, leading to an accumulation of negative treatment burdens on the patient. It also transformed clinical practice for retinal ophthalmologists, creating entirely new business models where multiple days a week are spent doing long strings of IVT, delivering as many as 60 or more injections per day per ophthalmologist (in the US).

In the 2020s, there has been an increasing focus on innovation and optimisation to begin to address the growing number of patients missing appointments and abandoning IVT regimens entirely. These innovations have focused on reducing injection frequency via different formulations and durations, improving clinical workflows and other ways of supporting long-term adherence.

Among the accumulated stack of issues pushing patients away from IVT, the heightened emotional anxiety felt around the injection itself has the strongest negative impact. These highly emotional aspects can be made far less intimidating through a combination of improved technology, human factors considerations and product design. However, the pathways to these patient-centric drug delivery improvements present substantial structural and business model hurdles.

WHAT ARE THE PATIENT BURDENS?

From the patient's perspective, IVT is defined by two dominant challenges – the time it takes and the anxiety it produces. However, a look at the complex interplay of factors that impact patient experience

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Patient Experience	Cause
Pain or irritation	• Chemical irritation • Mechanical irritation • Spike in IOP
Visual disturbance	• Vitreous opacities (floaters) • Turbulence and air bubbles
Bloodshot eyes	• Burst blood vessel
Affected vision or blindness	• Endophthalmitis (infection) • Traumatic cataract • Retinal detachment

Table 1: Potential side-effects.

shows that there is no simple "silver bullet" solution (Figure 1 & Table 1). Addressing the discontinuation of treatment will therefore require significant systemic changes both to the patient journey and clinical workflow. Some of the factors causing patients to discontinue therapy and which add to the levels of patient fear and anxiety include:

- **Process Inconsistency:** There is no one standard method or process for implementing IVT – changes in process trigger heightened emotions
- **Needle in the Eye:** The experience of the bare needle is frightening
- **Speculums:** Most clinics use speculums for keeping the eye open, exacerbating the sense of helplessness and impending danger for patients
- **Fixation:** Patients' own involvement in holding their eye steady during the injection process is frightening – they feel responsible for possible serious injury to the eye
- **Subconjunctival Haemorrhaging:** "Red Eye Roulette" happens in an estimated 10% of injections, can last for weeks and can cause embarrassment and social isolation until it resolves
- **Increased Intraocular Pressure (IOP):** Heavy eye and eye discomfort are the short-term issues of increased IOP, and repetitive or prolonged pressure on the optic nerve can cause more serious long-term visual degradation
- **Multiple Steps:** IVT delivery requires many steps, including antiseptic and anaesthetic, which prolongs the process, offers additional discomfort and is often messy
- **Side-Effects:** Patients often fear critical side-effects, such as endophthalmitis, as well as other non-critical ones
- **Logistics:** Other significant burdens less tethered to the drug delivery process itself include travel time, the need for caregiver support, injection frequency and cost.

HAVE RECENT INNOVATIONS HELPED?

The primary focus of innovation has been reducing the frequency of injections, and there has been a proliferation of innovative pharmacological variations and drug delivery systems that champion the value of greater durability. Durability, in this context, refers to how long the therapy remains active in patients after a dose is delivered. Logically, when a dose of therapy lasts longer, patients will require fewer, less frequent trips to the clinic – this should result in a reduced patient burden and significantly fewer therapy discontinuations over time. Some remarkable devices have been and continue to be developed to help deliver more durable solutions, including port delivery, implants and gel-centric technologies.

To understand the impact of these remarkable innovations, studies have aimed at assessing the association between treatment interval and the likelihood of patients discontinuing anti-VEGF treatment. What these studies have revealed is surprising. Real-world studies (including Bakri *et al*, 2022[1]) looking at injection schedules and long-term treatment behaviours have shown that less frequent injections do not automatically lead to better patient follow-through. In fact, one study found that some groups of patients who were moved to 12-week or longer intervals were more likely to stop treatment than those who continued on shorter schedules.

While further research is needed, received wisdom suggests that when patients come in less often, they may feel that their disease is stable or may simply lose the routine of ongoing care. Therefore, even though longer-lasting treatments help reduce the burden of clinic visits, it is possible that greater durability alone is not enough to keep patients adherent. Other permutations of durability might offer better results. If, for instance, there were just a single one-and-done injection – as promised by some gene therapies – that would certainly be a winner. Short of that, effective care will require addressing the burdens more holistically.

WHAT DOES HOLISTIC MEAN IN THIS CONTEXT?

A more patient-centric IVT delivery device and associated workflow will only be seen as a great innovation when it elegantly integrates into the wider set of success factors. Furthermore, lowering the patient burden may or may not be enough to substantially lower the discontinuation rate, as the patient burden is just one of the critical puzzle pieces in the overall IVT stakeholder ecosystem. The next generation of IVT drug devices must fit

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"AN IVT DEVICE SOLUTION THAT TRULY ACCOMMODATES THE SYSTEM-LEVEL REQUIREMENTS IS NOT LIKELY TO BE A CONVENTIONAL 'BETTER NEEDLE' OR INCREMENTAL IMPROVEMENT OF THE INJECTION DEVICE."

into a broader and dynamic ecosystem shift while also making non-adherence a much less common outcome. An IVT device solution that truly accommodates the system-level requirements is not likely to be a conventional "better needle" or incremental improvement of the injection device – it will have to function as a system-enabling device that simultaneously changes clinical confidence, workflow economics, patient burden and reimbursement logic.

WHO ARE THE STAKEHOLDERS IN THE IVT ECOSYSTEM?

There are quite a few stakeholders involved in a holistic IVT solution – some wielding more clout than others. The primary stakeholders are:

- Patients
- Clinics and practices
- Private equity
- Value-based health systems
- Insurers and payers
- Pharma companies
- Device companies
- Ophthalmologists.

A device design that benefits all IVT stakeholders must overcome a number of divergent – and sometimes contradictory – goals (Figure 2). Some of these include reducing patient burden, preserving clinical flexibility, maintaining clinic economics, protecting pharma value, satisfying payer cost logic and scale within existing health system workflows. Understandably, each set of stakeholders has different priorities, and these do not all point to the same solutions. A device that truly "works" for IVT must resolve most, if not all, of these structural conflicts.

When looking at the IVT delivery challenge from the separate stakeholders' perspectives, solutions could quickly lead in different directions:

- **Patients:** Want to reduce their lived burdens by lowering anxiety without increasing risk. Patients value reliability, predictability and the user experience as much as having fewer injections.
- **Clinicians:** Want to preserve clinical control and flexibility. Clinicians are very reluctant to change their process.
- **Practices:** Want to protect economic sustainability while improving clinic throughput. Clinics will adopt burden-reducing solutions only if the economics remain neutral or positive.
- **Pharma Companies:** Want to protect value while enabling differentiation. Pharma companies will support devices that reframe durability as value, not lost volume.

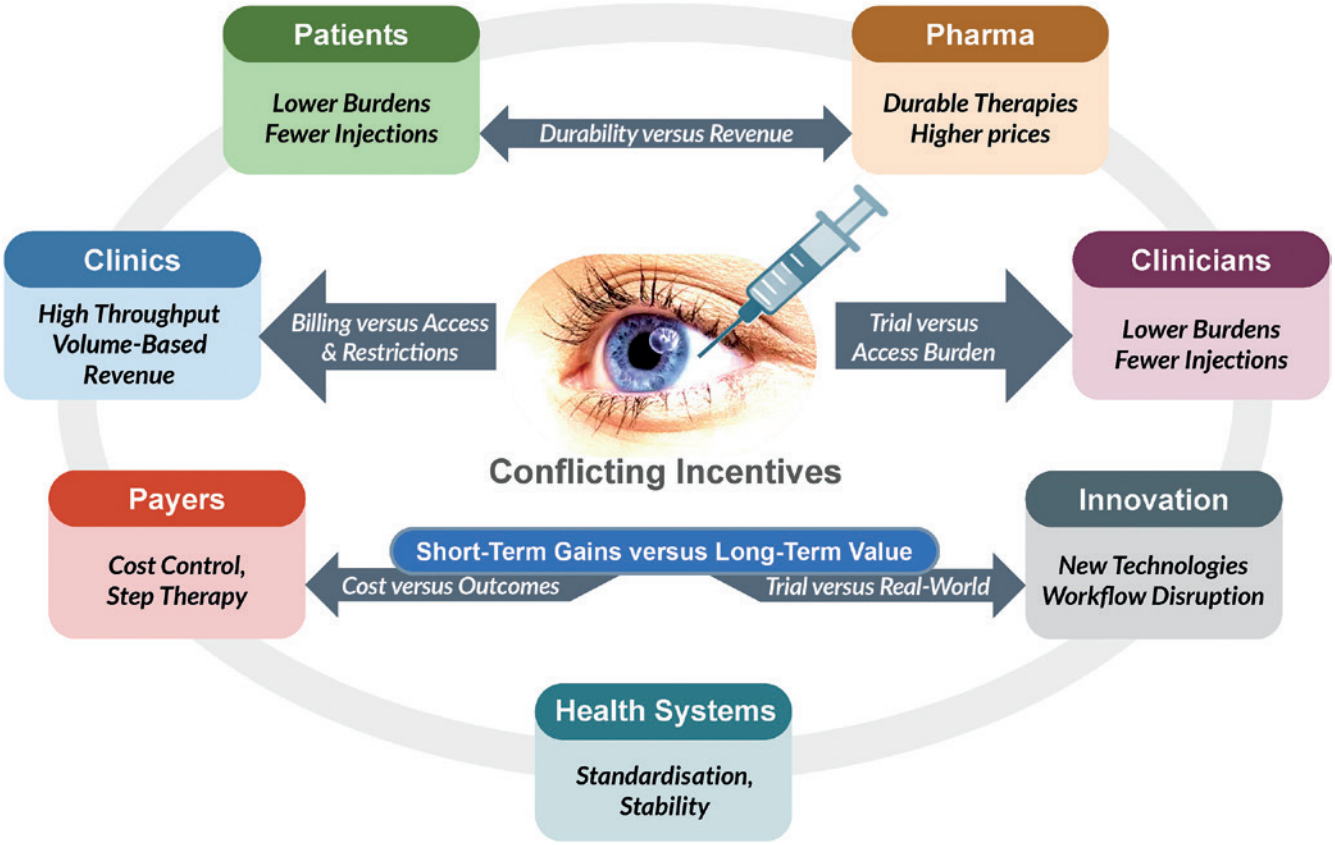


Figure 2: Inherent conflicts within the IVT ecosystem.

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- **Payers:** Want to reduce the cost of care. Payers value predictable, measurable evidence, not novelty.
- **Healthcare Systems:** Want to standardise procedures, minimise training and reduce bottlenecks. Healthcare systems care about maintaining stability while improving care delivery.
- **Device Innovators:** Want to quietly resolve conflicts between other stakeholders. For device developers, economic benefits drive adoption, but patient safety, enhanced workflows and more ideal usability motivate change.

WHERE TO START?

Mapping and keeping track of all these variables (Figure 3) is very important – but knowing when each stakeholder group should be considered is fundamental to finding a way forward. One common set of factors that all stakeholders must support is that the therapy is safe, effective and not alienating for patients. Therefore, the starting point for finding better solutions begins with developing a deep, holistic understanding of each of the pain-points, burdens and side-effects.

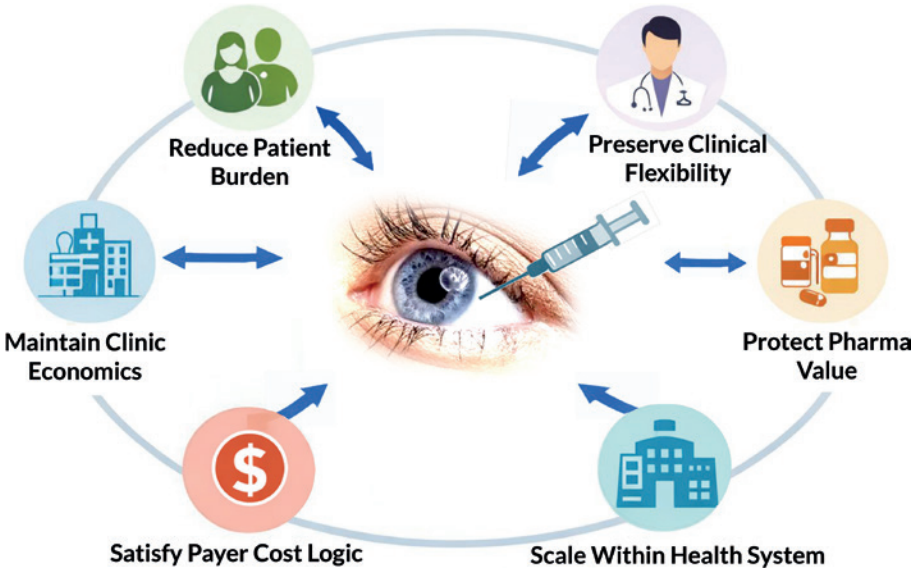


Figure 3: Future IVT devices must simultaneously benefit multiple stakeholders with conflicting priorities.

To get there, design teams must attempt to prioritise the user experiences that are often muddled together under headings such as fear, anxiety and pain, after which they can begin developing potential solutions to eliminate or minimise enough of these negative, alienating aspects to have a profound impact on the patient experience. Once a carefully designed solution – one that will keep a significant percentage of otherwise disenfranchised patients engaged in treatment – has been prototyped and tested with patients and a set of key initial stakeholders, it will then need to be tuned and refined to accommodate the needs of the remaining stakeholders within the IVT ecosystem.

"THE STARTING POINT FOR FINDING BETTER SOLUTIONS BEGINS WITH DEVELOPING A DEEP, HOLISTIC UNDERSTANDING OF EACH OF THE PAIN-POINTS, BURDENS AND SIDE-EFFECTS."

ABOUT THE COMPANY

Fearsome is a contract design and development company working with clinicians and medtech and biopharma clients to realise innovative medical devices. Established in 2002, the company provides comprehensive, end-to-end services focusing on high-risk devices and targeted drug delivery systems. Its multidisciplinary team is experienced in ocular and neurosurgical programmes.

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Gregg Draudt

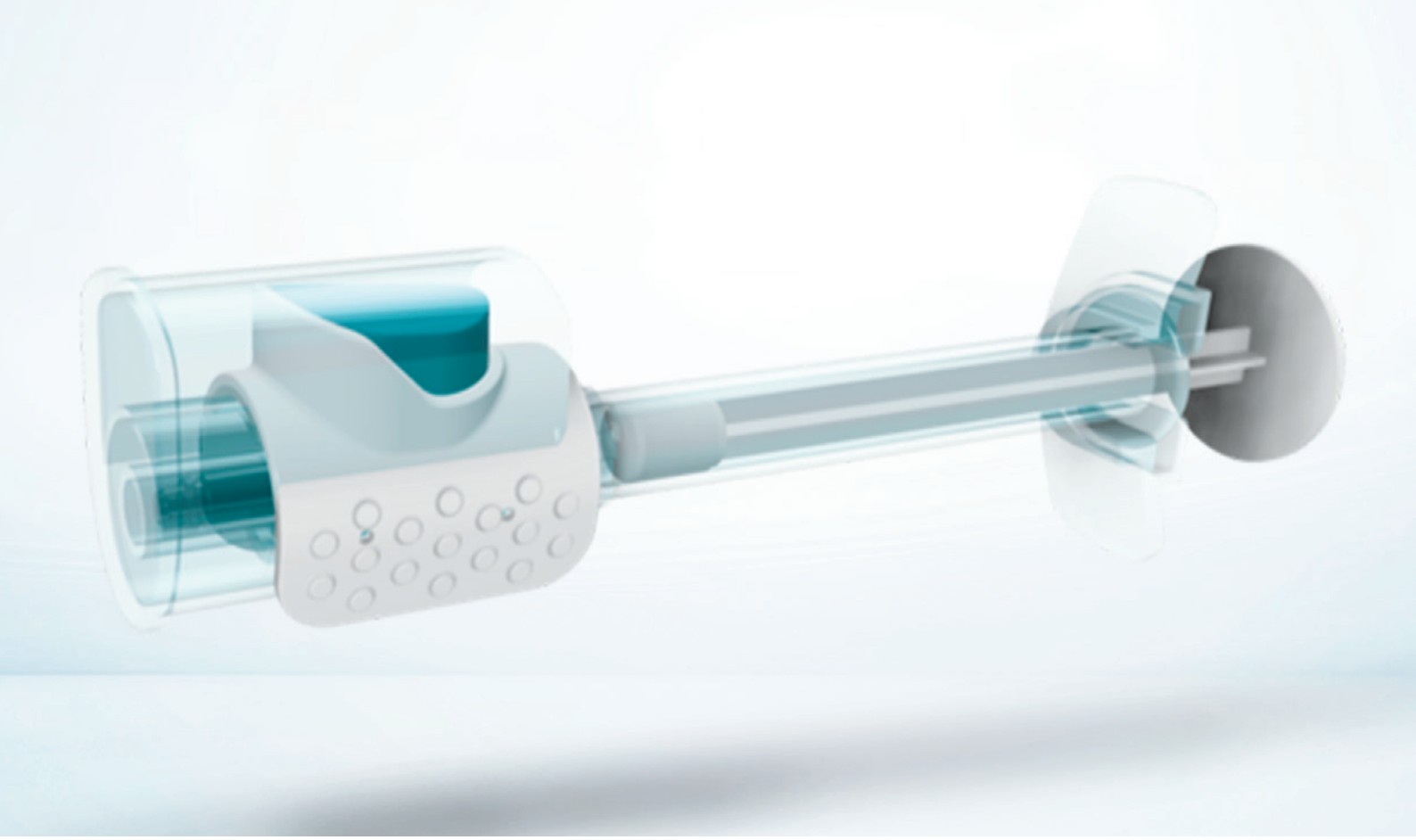
Gregg Draudt is a MedTech Innovation Leader at Fearsome whose early career focused on hands-on invention, resulting in more than 50 issued utility patents. Today, he concentrates on client relationship management and guiding multidisciplinary teams through complex medical device development programmes.

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BRAND NEW TITLE LAUNCHING 2027 ON diagnostics

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SHL MEDICAL AND BAYER: A COLLABORATIVE APPROACH TO ADVANCING INTRAVITREAL PAEDIATRIC DOSING

Andreas Kalitzki of **Bayer** and **Samuel Wyler** and **Dr Seda Aksel** of **SHL Medical** explain how the companies' collaborative efforts are enhancing paediatric intravitreal injections through evidence-based dosing strategies and clinically validated therapies using SHL Medical's Micro Dosing Device technology.

The clinical use of intravitreal therapies (IVTs) has seen steady growth, particularly in response to rising rates of sight-threatening conditions such as age-related macular degeneration, diabetic retinopathy and retinopathy of prematurity (ROP). These conditions often require localised injections directly into the vitreous body of the eye, where the precision of both the drug and its delivery play a central role in patient outcomes.

ROP is a disease of retinal vascular development that occurs in premature infants. It is characterised by the abnormal growth of immature retinal blood vessels, which can progress to fibrovascular proliferation, retinal detachment and ultimately blindness if untreated.[1]

Low birth weight under 1,500 g (3.3 lb) and early gestational age (<32 weeks) are the major risk factors for

"THE CLINICAL USE OF IVTs HAS SEEN STEADY GROWTH, PARTICULARLY IN RESPONSE TO RISING RATES OF SIGHT-THREATENING CONDITIONS SUCH AS AGE-RELATED MACULAR DEGENERATION, DIABETIC RETINOPATHY AND ROP."

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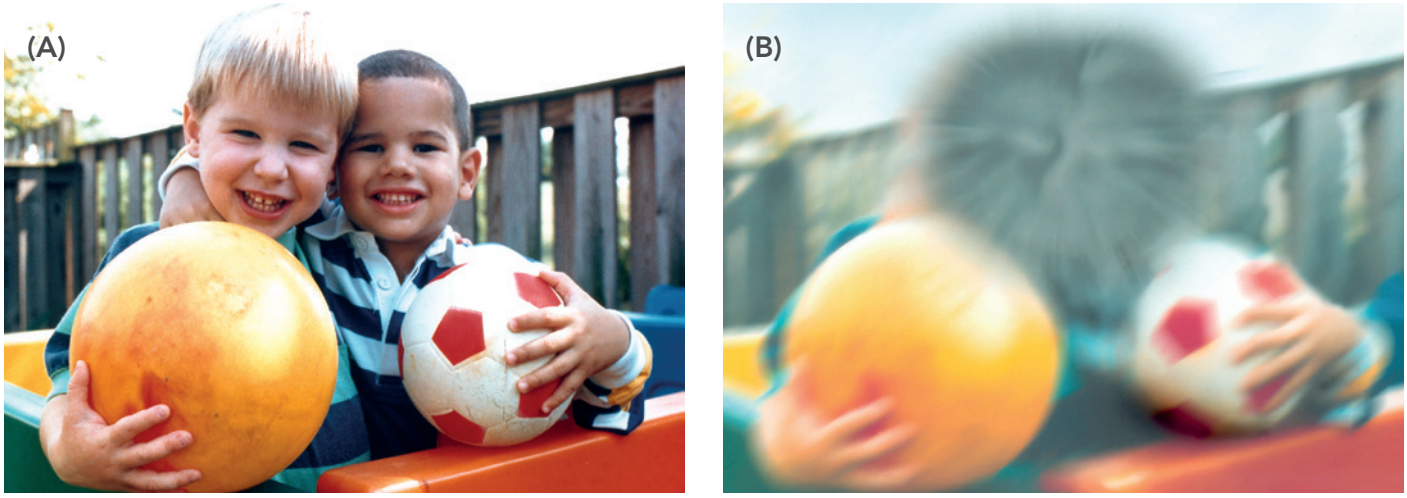


Figure 1: (A) Normal vision and (B) vision affected by macular degeneration. Image courtesy of the National Eye Institute, National Institutes of Health (Public domain).

ROP, making it one of the leading causes of childhood blindness worldwide. In the UK, ROP screening is performed in preterm infants who meet these risk criteria. A 2011 UK cohort study reported an incidence of 12.6% in this population, and rates have continued to rise globally as the survival of smaller preterm infants improves.[2–4]

ROP is a complex retinal vascular disease, often developing in two overlapping phases:

1. **Phase I (Hyperoxia-Induced Vessel Cessation)**: Preterm infants often receive supplemental oxygen, which halts the normal development of retinal blood vessels by suppressing angiogenesis driven by vascular endothelial growth factor (VEGF). This leads to large areas of avascular peripheral retina.
2. **Phase II (Hypoxia-Induced Pathological Neovascularisation)**: As the retina matures, it becomes hypoxic in those avascular zones. The resulting surge in VEGF triggers the growth of fragile, disorganised new blood vessels. These vessels may leak, form fibrovascular membranes and cause retinal traction or detachment.

If left untreated, the advanced stages of ROP can lead to retinal detachment and lifelong vision loss (Figure 1).

ROP severity is classified according to the International Classification of ROP (ICROP). These diagnostic categories classify ROP based on:

- **Location (Zone)**: Zones (I–III) describe the anatomical location of disease within the retina. This is illustrated in Figure 2A.

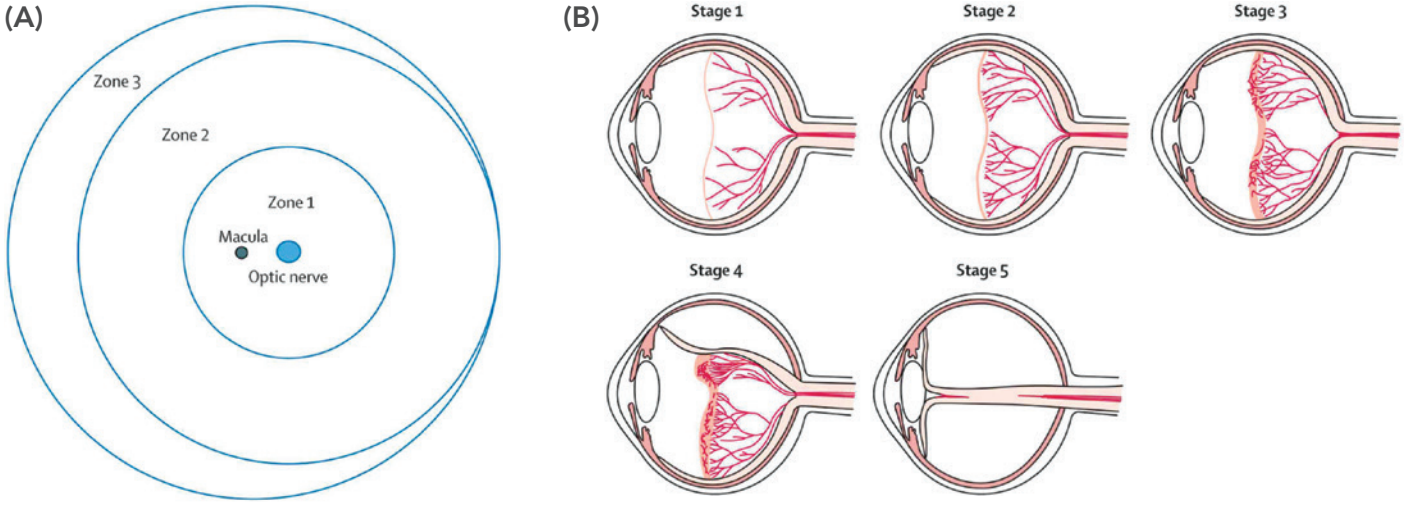


Figure 2: Zones and progressive stages of ROP. Figure A shows that the retina is divided into three zones. Figure B illustrates the classification of ROP according to stages: Stage 1 ROP – A faint demarcation line marks the boundary between vascularised and avascular retina; Stage 2 ROP – The line becomes a ridge, indicating abnormal vascular proliferation; Stage 3 ROP – Extraretinal fibrovascular proliferation extends into the vitreous, increasing the risk of retinal detachment; Stage 4 ROP – Partial retinal detachment; and Stage 5 ROP – Total retinal detachment. Reproduced from Retinopathy of Prematurity—A Brief Review by Saba Al Rashaed, licensed under CC BY 4.0.

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- **Severity (Stage):** Stages (1–5) reflect the severity of retinal changes, ranging from Stage 1 (a demarcation line) to Stage 5 (total retinal detachment). This is illustrated in Figure 2B.

- **Posterior Pole Vascular Features (Normal, Pre-Plus or Plus Disease):** Plus disease is a hallmark of aggressive ROP, where retinal vessels show marked dilation and tortuosity. It is a sign of worsening pathology and indicates a high risk of progression to more severe ROP. Its presence often signals the need for immediate treatment.[5,6]

EYLEA® (aflibercept – Regeneron Pharmaceuticals, Tarrytown, NY, US), a recombinant fusion protein designed to bind VEGF-A, VEGF-B and placental growth factor, has established its role as an effective and targeted therapy for ROP. Its ability to inhibit multiple angiogenic factors makes it particularly suitable for severe or aggressive cases of ROP. Importantly, its use in this indication is gaining traction following results from randomised clinical trials, such as the Phase III study FIREFLEYE, which demonstrated encouraging regression rates in infants with treatment-requiring ROP.[7]

In the treatment of ROP, especially with anti-VEGF agents such as aflibercept, the precision of the administered dose is critical – both for therapeutic success and to minimise risk. The recommended intravitreal dose for ROP is 0.4 mg per eye, corresponding to a volume of 10 µL. Delivering a precise microlitre-scale volume is inherently challenging, and small deviations can lead to under-treatment (risking recurrence) or over-treatment (increasing intraocular pressure and systemic complications).

Data from ongoing trials and real-world case series show that recurrence of ROP is significantly reduced when aflibercept is delivered at the appropriate dosage with strict control over injection volume and technique. For example, in the FIREFLEYE study, treatment with aflibercept 0.4 mg led to high regression rates and minimal systemic VEGF suppression – provided the injection volume was carefully calibrated.[7]

Studies have also shown that administration with syringes – such as 1 mL disposable syringes or glass prefilled syringes (PFSs) – often exhibit significant variability when delivering microlitre doses. This variability becomes clinically significant when the therapeutic margin is narrow, as is the case with aflibercept in neonatal ROP. Developed by SHL Medical in partnership with Bayer, Picleo® is helping to deliver the precise volume for the paediatric preterm indication, without significantly changing the IVT process in terms of injection workflow.[8,9]



Figure 3: Image inset of EYLEA® (aflibercept) and the Picleo® paediatric dosing device. The device enables high dosing accuracy volumes as low as 10 µL.

THE PICLEO® PAEDIATRIC DOSING DEVICE

The Picleo® paediatric dosing device is specifically designed to ensure safe and reliable intravitreal delivery of EYLEA in preterm infants (Figure 3). Developed based on SHL Medical's Micro Dosing Device (MDD) technology, the device is compatible with standard Luer lock PFSs and needles via Luer lock interfaces. Key features of the device include:

- **Fixed-Dose Volume Delivery:** Engineered to administer a precise nominal dose – drastically reducing variability seen with conventional syringes[10]
- **PFS Compatibility:** Designed to directly accommodate Bayer's EYLEA® (aflibercept 40 mg/mL) PFS with Luer lock connection and a 30G needle, ensuring a closed, controlled system during preparation
- **Ease of Preparation and Safety:** The device includes a visual window for priming, explicit instructions to eliminate air bubbles (which are a potential cause of underdosing) and ergonomic grips to hold the device, preventing accidental actuation
- **Ease of Administration:** One-click dosing mechanism – the dose button delivers the fixed volume, with no need for dose mark alignment, eliminating human errors in microlitre dosing
- **Regulatory Compliance:** Compliant with EU Medical Device Regulation (MDR 2017/745) and intended for ROP administration; provided sterile for single use to reduce the risk of infection.

"THE PICLEO® PAEDIATRIC DOSING DEVICE IS SPECIFICALLY DESIGNED TO ENSURE SAFE AND RELIABLE INTRAVITREAL DELIVERY OF EYLEA IN PRETERM INFANTS."

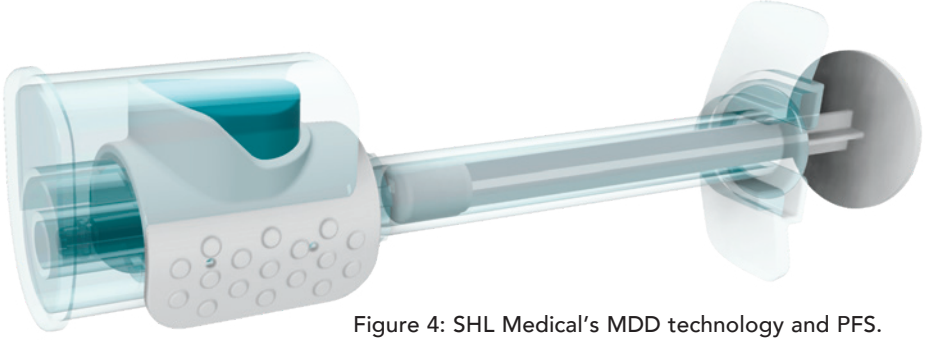


Figure 4: SHL Medical's MDD technology and PFS.

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Specification	SHL & Bayer's Picleo Device
Device Type	MDD
Primary Container	Disposable or PFS with standard Luer lock connection
Usage	Single fixed-dose, disposable
Needle Attachment	Manual, compatible with conventional hypodermic needles with female Luer lock connector
Syringe Attachment	Manual, compatible with syringes with male Luer lock connector
Route of Administration	Subcutaneous, intravenous and intravitreal
Injection Feedback	Audible click at the end-of-dose, visual and tactile feedback

Table 1: Technical specifications of SHL Medical's MDD technology.

The MDD technology (Figure 4) developed by SHL Medical is designed to enable the accurate, repeatable delivery of fixed microlitre-scale drug volumes. This is independent of user technique, addressing the inherent limitations of conventional syringes at very low doses. To use the MDD, it is first attached between the PFS and an injection needle. The plunger rod is slowly depressed to prime the system, expelling any air and filling the chamber within the device. The push button is subsequently used to mechanically deliver the controlled volume, thereby minimising variability associated with applied hand force, visual dose alignment and syringe tolerances. An overview of the specifications of the device can be seen in Table 1.

DOSING PERFORMANCE EVALUATION

A comparative analysis was conducted to assess the dosing accuracy of the MDD in combination with a PFS versus a disposable syringe with a visual indicator to establish a 10 µL dose.



Figure 6: Handling technique during a simulated injection with the Picleo paediatric dosing device.

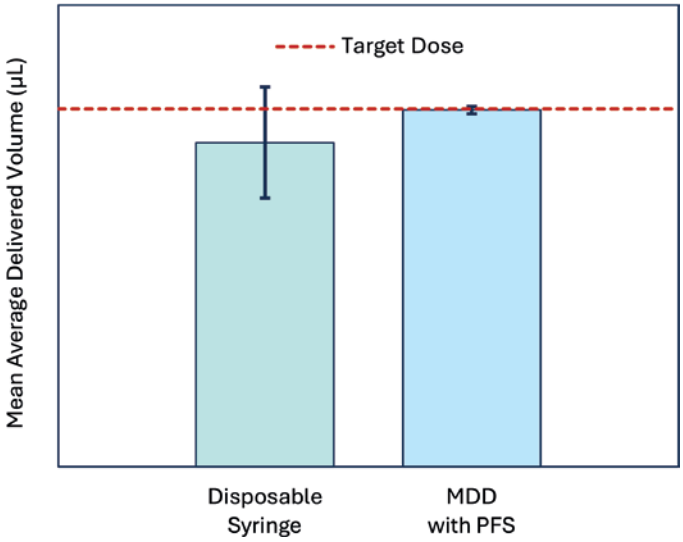


Figure 5: Comparison of dose accuracy achievable with a conventional syringe and the MDD technology.

Both delivery systems were filled with aflibercept (40 mg/mL) and used a 30G x ½" injection needle. The study focused on key metrics such as dose accuracy and repeatability.

The baseline dataset generated with the conventional disposable 1 mL syringe showed a high standard deviation of 2.09 µL, indicating substantial user-dependent variability and poor task-to-task consistency. In contrast, the dataset obtained with the MDD exhibited a mean value closely aligned with the target and a markedly lower standard deviation of 0.13 µL. The higher accuracy, improved repeatability and superior procedural control is illustrated by the difference between the error bars shown in Figure 5.

The results from a statistical comparison using a two-sample t-test ($t = -4.65, p < 0.0001$) confirmed that the performance difference was significant. These findings provide strong evidence that the MDD offers substantial usability advantages over the conventional syringe method. The marked reduction in variability and improved alignment to target values indicate that the MDD's design enables more intuitive operation, finer dose control and a lower likelihood of user error.

FORMATIVE USABILITY TESTING

A usability study (Figure 6) was conducted to evaluate the safe and effective use of the Picleo® paediatric dosing device for administering IVTs in premature infants with ROP. The study involved six experienced ophthalmologists in Germany and was designed as a face-to-face, simulated-use study that replicated a neonatal intensive care unit or operating room environment. Each participant performed a full injection workflow using a placebo-filled PFS and a 30G x ½" injection needle, simulating administration into dummy eyes mounted on a model infant. The procedure included unpacking the product, reviewing the instructions for use, assembling and priming the system, and performing a simulated injection. Hand size and grip strength were also measured to assess ergonomic factors. The results of this study confirmed the overall comprehensibility, adequacy and acceptability of the system and

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its accompanying instructions. The usability evaluation provided objective evidence that the device can be used safely and effectively by the intended users.

CONCLUSION

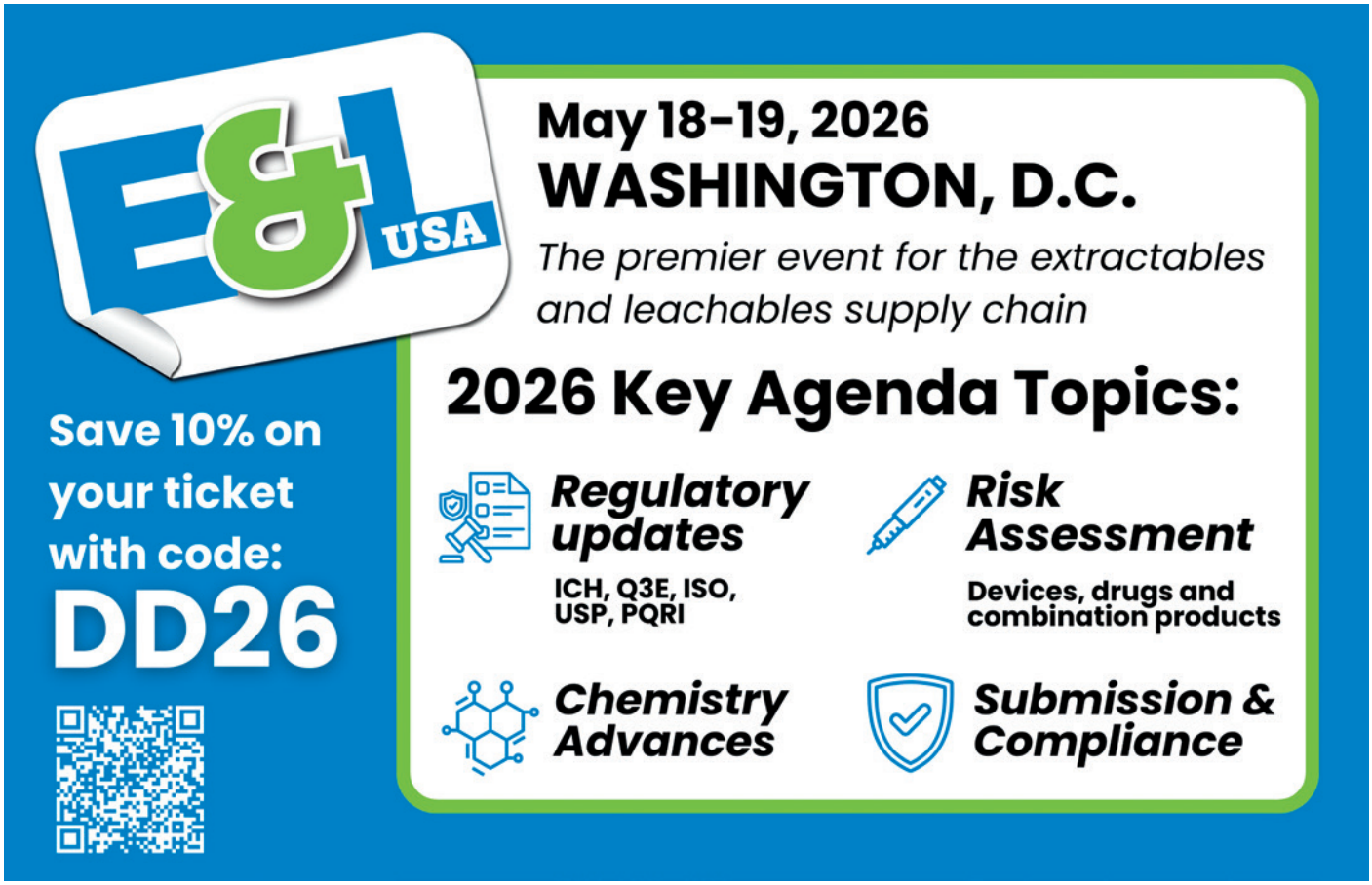
The successful treatment of ROP hinges on achieving a delicate balance: delivering an effective dose while minimising ocular and systemic risk in an extremely vulnerable patient population. Bayer's continued efforts in paediatric retinal disease reflect a clear commitment to addressing this unmet medical need through evidence-based dosing strategies and clinically validated therapies such as aflibercept. By enabling reliable administration of the recommended low dose and small injection volume without fundamentally altering the established IVT workflow, Bayer supports both therapeutic precision and clinical practicality – two essential factors for adoption in neonatal care settings.

At the same time, SHL Medical's MDD technology represents a broader vision for precision drug delivery beyond intravitreal use. Designed as a flexible solution, the MDD has the potential to add value across multiple therapeutic areas where fixed, low-volume dosing is critical and conventional delivery systems fall short. Collaboration between device companies and pharmaceutical partners can bridge the gap between therapies and those who need them, enabling safer, more precise dosing and improved patient outcomes.

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"THE SUCCESSFUL TREATMENT OF ROP HINGES ON ACHIEVING A DELICATE BALANCE: DELIVERING AN EFFECTIVE DOSE WHILE MINIMISING OCULAR AND SYSTEMIC RISK IN AN EXTREMELY VULNERABLE PATIENT POPULATION."



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EMPOWERING VISION FOR THE FUTURE: ADVANCED CONTAINMENT SOLUTIONS FOR OPHTHALMIC APPLICATIONS

Dr Linara Cornell, **Dr Manali Potnis** and **Dr Krishnendu Khan**, all of **West Pharmaceutical Services**, review the current landscape and challenges associated with delivery systems for ophthalmic applications, and how West Pharmaceutical Services plays a critical role in this specialised industry by providing high quality prefilled syringe components and systems that meet the stringent requirements for these sight-saving therapies.

Ophthalmic drug delivery has evolved rapidly over the past two decades, driven largely by the success of injectable biologics targeting retinal diseases such as age-related macular degeneration, diabetic retinopathy and diabetic macular oedema. The widespread adoption of intravitreal injections (IVIs) has transformed patient care by stabilising or even improving vision in previously untreatable conditions. Each injection requires precision, sterility and consistency to maintain safety and visual outcomes.

This heightened focus has accelerated the transition from traditional vial-and-syringe preparations to ready-to-administer delivery formats, such as prefilled syringe (PFS) systems, which reduce contamination risks, improve workflow efficiency and ensure consistent dosing accuracy. Consequently, the design of the PFS plays a pivotal role in reducing procedural

"MODERN OPHTHALMIC PFS SYSTEMS HAVE EVOLVED SIGNIFICANTLY TO MEET THE STRINGENT DEMANDS OF INTRAVITREAL AND PERIOCULAR DRUG ADMINISTRATION, PARTICULARLY FOR THERAPIES DELIVERED IN MICROVOLUMES."

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complexity and clinician workload. Importantly, the use of PFSs has been associated with a lower risk of post-injection endophthalmitis[1-3] (a severe infection and inflammation of the inner eye).

Within this context, PFSs have become critical primary container systems for ophthalmic applications, streamlining clinical workflows while enabling reliable, sterile and patient-focused injection experiences.

CURRENT LANDSCAPE FOR OPHTHALMIC SYRINGES

Syringe Formats, Materials and Emerging Trends

Modern ophthalmic PFS systems have evolved significantly to meet the stringent demands of intravitreal and periocular drug administration, particularly for therapies delivered in microvolumes. A typical PFS assembly comprises several key components, including the barrel, plunger or piston, plunger rod, needle, and tip cap or needle shield. Of these, the barrel and plunger are of paramount importance, as they directly contact the drug product and largely determine the system's compatibility, stability and performance.

Ophthalmic PFSs are available in both glass and polymer formats, each offering distinct advantages depending on the drug formulation and intended storage conditions. Glass syringes remain the most established material due to their long regulatory history, excellent barrier properties and compatibility with a wide range of biologics. However, glass syringes can also present certain challenges, including potential interactions with silicone oil lubricants,[4] residual tungsten generated during the needle manufacturing process and susceptibility to breakage,[5] all of which are critical considerations for sensitive ophthalmic therapies administered in microvolumes.[6,7] Another significant concern is glass delamination, where thin lamellae or flakes detach from the inner wall following chemical interactions with high pH or ionic formulations.[8] Moreover, certain molecules, particularly proteins, can adsorb to the charged surface of glass, which may reduce the drug's potency.[9]

In contrast, polymer syringes made up of cyclo-olefin polymer (COP) or cyclo-olefin copolymer materials have gained traction as a modern alternative, offering low extractables and leachables (E&L) profiles, high break resistance and flexible design. Polymer syringes are also free of tungsten and metal ions, reducing compatibility concerns for fragile formulations, particularly protein-based therapeutics. Moreover, polymer syringe systems enable features such as silicone-free or silicone-based lubrication technologies that can further minimise particle generation and protein aggregation.

Beyond material selection, ophthalmic PFS systems can be configured with either Luer lock or staked-needle options, each providing distinct advantages depending on clinical and formulation needs. Staked-needle syringes offer a fully integrated design that simplifies assembly, maintains sterility and ensures accurate, ready-to-use administration – attributes especially valuable for single-use IVIs. Luer lock configurations, however, offer flexibility during development, allowing attachment of different needle types or connectors, which is beneficial for early formulation screening or specialised delivery procedures.

This focus on minimising interactions extends to the plunger system, which plays a critical role in both drug compatibility and device performance. Modern bromobutyl and chlorobutyl plungers are designed to provide enhanced chemical and physical resistance, along with high manufacturing consistency. Each elastomer type exhibits a distinct E&L profile, which might be further influenced by the barrier layer that is sometimes applied to the drug-contact surface. Depending on the design, these barriers may coat only the drug-contact area or cover the entire plunger. Common barrier technologies include film-based laminations and thin, functional coatings applied through spraying, lamination or other deposition methods.

Some specialised barrier layers include silicone, B2, Teflon®, FluroTec™ or OmniFlex®. These surface treatments help to maintain formulation stability, reduce E&Ls and improve the functional reliability of the plunger system. These surface treatments serve several purposes:

"STABILITY STUDIES ARE CONDUCTED TO CONFIRM THE PURITY AND POTENCY OF THE DRUG UNDER DEFINED STORAGE CONDITIONS, WHILE BIOCOMPATIBILITY TESTING ENSURES THAT MATERIALS IN CONTACT WITH THE DRUG OR PATIENT TISSUES ARE SAFE AND NON-REACTIVE."

they reduce E&L levels, maintain formulation stability, improve glide and break-loose forces, and can also enhance container closure integrity (CCI). Achieving optimal performance requires precise matching of material, geometry and surface characteristics. This is especially critical in ophthalmic applications, where microdose accuracy and sensitivity of biologic formulations demand exceptional control over all syringe components.

The plunger rod is considered a secondary packaging component, as it does not directly contact the drug formulation. It is commonly manufactured from polypropylene due to the polymer's strength, chemical resistance and ease of processing.[10]

Regulatory Considerations

The US FDA and the EMA tightly regulate ophthalmic products, including small-molecule drugs, biologics and medical devices used in or around the eye. When an ophthalmic product is packaged in a PFS, additional considerations arise, as this format introduces several potential challenges. These include compatibility between the formulation and syringe components, as well as mechanical performance factors, such as CCI, dose accuracy and ease of use. Stability studies are conducted to confirm the purity and potency of the drug under defined storage conditions, while biocompatibility testing

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ensures that materials in contact with the drug or patient tissues are safe and non-reactive. Regulations also mandate clear labelling and instructions for handling, preparation and administration to ensure consistent and safe use by healthcare professionals and patients alike. Even after regulatory approval, the FDA requires post-market surveillance, which includes the collection of adverse event data, periodic inspections and continued verification that the product remains compliant with all applicable safety and quality standards.

One potential concern for PFSs in ophthalmic applications is the risk of particulate contamination originating from syringe materials. The regulatory framework for particulates in ophthalmic injectables is defined by the US Pharmacopeia (USP) Chapter <789>, which outlines official methodologies for testing and acceptance criteria for visible and subvisible particulates in injectable ophthalmic products. Testing includes light obscuration particle count and microscopic particle count. This chapter mandates that all ophthalmic products must undergo visual inspection and that injectable solutions must be free of foreign matter.

The European Pharmacopoeia (EP) further distinguishes between extrinsic and intrinsic particles. Extrinsic particles typically originate from the environment, equipment or packaging, while intrinsic particles arise from the formulation or product itself. Although both types must generally be avoided, some particles – such as those intentionally included in cell therapies – may be acceptable if measures are taken to ensure no unintended particles are present. The EP also notes that certain products can be difficult to inspect visually due to properties such as opalescence, colouration, opacity or lyophilisation. In such cases, additional testing is required, including extended inspection times against black and white backgrounds or the use of higher light intensities.

Generally, both the FDA and EMA recommend risk-based control strategies, building quality into processes to prevent particulates from sources such as manufacturing, packaging and the drug itself, especially because ophthalmic particles can cause "floaters" or irritation.

CURRENT TECHNICAL CHALLENGES FOR OPHTHALMIC SYRINGES

Particulates

Particulates are tiny, unwanted, undissolved solid particles found in injectable medicines that can negatively impact patients by causing inflammation, blockages or immune reactions. In ophthalmology, particulates can contaminate eye medications, not only posing a high risk of reduced drug efficacy but also of serious adverse effects, including ocular tissue damage, vision impairment and endophthalmitis. Large particulates may also affect injection smoothness and precision by increasing the required injection force.

The issue of particulates is regulated by USP <789>, which specifies strict limits on the number of particles of different sizes. In ophthalmic formulations, most particulate contamination originates from silicone oils released from syringe barrels. These can promote protein aggregation and the formation of protein-based particles. Additionally, manufacturing debris, such as residual tungsten or glass lamellae, can contribute to particulate contamination.

To reduce the formation of silicone oil-based particles, novel siliconisation techniques have been developed, including baked-on or cross-linked silicone coatings. Glass syringes with baked-on silicone are made by heating the siliconised glass barrel, vapourising the low-molecular weight silicone molecules and further immobilising the coating. Crosslinking allows for a stronger chemical bond between the silicone layer and the barrel, which reduces silicone migration into the solution.[11] However, these methods do not completely eliminate the problem. Therefore, silicone-free syringes remain the most effective solution for preventing silicone-related particulates, although they require careful design to ensure consistent injection smoothness.

"ONE OF THE MOST CRITICAL CONSIDERATIONS IN PFS DESIGN IS ENSURING THAT THESE COMPONENTS DO NOT INTRODUCE E&LS DURING CONTACT WITH THE PRODUCT."

Extractables & Leachables

One of the most critical considerations in PFS design is ensuring that these components do not introduce E&Ls during contact with the product. The presence of foreign chemical contaminants can compromise drug quality and efficacy and, more importantly, pose significant safety risks to patients. Ophthalmic drug products are especially sensitive to even trace levels of leachables. One of the issues is that the drug product comes into direct contact with ocular tissues, without the benefit of the body's digestive or metabolic defence mechanisms that help process other types of medications. Additionally, ophthalmic drugs are typically administered as low-volume formulations, which can result in higher concentrations of contaminants if leachables are present.

Type I borosilicate glass, the most commonly used material for glass PFS barrels, contains a range of inorganic oxides, such as boron, silicon, calcium, sodium, potassium, iron and aluminium.[12] Migration of these elements into the formulation can lead to precipitation with buffering salts, shifts in pH and potential toxic effects due to metal accumulation – especially in patients with impaired renal function. Furthermore, glass PFS systems that incorporate staked needles often require the use of tungsten pins during needle fabrication. Residual tungsten can leach into the product, leading to unwanted protein aggregation, unfolding or denaturation – all of which may reduce the drug's therapeutic efficacy and trigger undesirable immune responses.[13]

In contrast, polymer-based PFS systems – such as those constructed using COP – pose a much lower risk of E&L generation, making them particularly well-suited for sensitive biologics and advanced therapies. In a 36-month leachables study involving water for injection stored in COP-based PFS barrels, no observable difference was found in the levels of organic extractables compared with glass barrels. However,

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the elemental extractable values were significantly lower for COP barrels than for glass, indicating a cleaner material profile and reduced risk of inorganic contamination.[14]

Silicone and Lubrication Control

Most conventional syringes use silicone oil lubrication to facilitate smooth plunger movement; however, studies have shown that silicone droplets can migrate into the drug formulation. In ophthalmic applications, this phenomenon poses unique risks, as the introduction of silicone oil into the vitreous humour has been associated with adverse effects such as myodesopsia, commonly known as "floaters". These floating particles, varying in shape and size, can impair visual comfort and, in severe cases, necessitate surgical intervention.[15] In addition to ocular concerns, the release of silicone oil during storage and transportation can also promote protein aggregation, potentially increasing the immunogenicity of biologic formulations.[16] To mitigate these risks, several silicone oil-free, polymer-based PFS systems have been developed in recent years. These designs employ alternative coatings or advanced surface treatments that deliver consistent, smooth injection performance while eliminating the adverse effects associated with silicone-based lubricants.

Performance Attributes

Additional factors influencing the selection of the most suitable PFS for ophthalmic applications include design and performance characteristics that affect usability – specifically, a clean, simple and secure needle attachment mechanism, as well as low and consistent glide forces to ensure smooth plunger movement. Equally important is the injection activation force (also known as break-loose force), which should be carefully optimised to allow the dose to be administered with minimal effort while preventing premature plunger activation during handling or transport. If the required forces are too high or inconsistent, jerky plunger motion may occur, potentially causing trauma to delicate ocular tissues.

Another critical parameter is the tissue penetration force. For instance, the sclera requires greater force for penetration than the cornea. Needle design and lubrication play significant roles in influencing both the tissue penetration force and the subsequent glide force during injection.[17] Injection rate and volume are also key considerations, as both can affect intraocular pressure. Properly managing injection forces helps to control flow rate and dose volume, reducing the risk of a sudden increase in intraocular pressure that could result in transient vision loss.[18]

Finally, the ergonomic design of the syringe should promote a comfortable, secure grip, enabling the user to easily control injection speed and positioning. The needle should remain safely shielded prior to activation to prevent accidental needlestick injuries, yet remain visible during use to allow healthcare professionals to confirm correct alignment and injection site placement.

Viscosity and Drug Formulation Considerations

Viscosity plays a pivotal role in determining injection forces, flow behaviour and overall delivery consistency in ophthalmic PFS systems. High-viscosity formulations can significantly increase the required injection force, potentially compromising injection smoothness and dosing precision. For intravitreal administration typically involving injection volumes of only 50–100 µL, small variations in force or flow rate can have clinically meaningful implications, such as transient intraocular pressure elevation or patient discomfort. Maintaining predictable flow characteristics is therefore critical for both safety and user experience. Syringe geometry, needle dimensions and plunger design must be optimised to achieve low and consistent glide forces even at elevated viscosities. Similarly, plunger coatings or surface treatments can reduce frictional resistance and maintain smooth movement throughout the injection stroke.

Material choice further influences performance. COP syringes, with their ultra-smooth internal surfaces and dimensional precision, have shown advantages in handling viscous ophthalmic formulations.[19,20] Their consistent friction profile supports controlled plunger movement and reproducible dose delivery, which are essential for IVIs given the small therapeutic window.



Figure 1: NovaPure® 0.5 mL plungers are designed for use with ISO glass syringes.

WEST PHARMACEUTICAL SERVICES' PRODUCT OFFERINGS

NovaPure® 0.5 mL Plungers

NovaPure® 0.5 mL plungers, developed by West, represent a next-generation elastomeric closure technology designed to ensure exceptional quality, consistency and compatibility for PFS applications, particularly those used for IVI therapies, where precision, purity and consistency are paramount. Manufactured using West's advanced bromobutyl rubber formulation 4023/50, NovaPure 0.5 mL plungers provide high chemical resistance, low E&L and dimensional uniformity. These properties help to mitigate the risk of interaction between the plunger and highly sensitive biologic formulations, supporting long-term drug stability (Figure 1).

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Key Product Attributes

- **Optimised Plunger Design:** Developed using quality-by-design principles to ensure consistent break-loose and glide force performance in ISO standard barrels for PFS applications.
- **FluroTec™ Barrier Film:** Minimises interactions between the drug formulation and the elastomeric closure, helping to maintain chemical stability and product integrity throughout shelf life.
- **Low Endotoxin:** Tightened endotoxin specification to 0.1 endotoxin units/device in alignment with FDA guidance on endotoxin testing recommendations for single-use intraocular ophthalmic devices and EP 5.1.10, ensuring enhanced patient safety of ophthalmic applications.
- **Low Particles:** Lowest particulate specification, for both visible and subvisible particulate, to enable alignment to USP <789> Particulate Matter in Ophthalmic Solutions.
- **MDR Package:** Comprehensive documentation, including relevant West technical summaries, quality statements, regulatory bulletins and exclusive supporting materials to facilitate compliance with Annex I of the European Medical Device Regulation (2017/745) filing requirements.

When paired with polymer or glass syringe barrels, NovaPure 0.5 mL plungers form an optimised containment and delivery system that minimises particulate generation and ensures reliable drug delivery performance over the product shelf life for ocular therapies. This, coupled with West's global supply and regulatory support network, enables pharmaceutical manufacturers to streamline development, reduce regulatory risk and ensure patient safety across the entire drug lifecycle.

Daikyo Crystal Zenith® Polymer Syringe

The Daikyo Crystal Zenith® (CZ) RU Luer lock 0.5 mL syringe is a sterile, ready-to-use PFS solution developed to meet the stringent requirements of modern biopharmaceutical and ophthalmic drug applications. This system offers break-resistant, superior particulate performance compared with conventional glass syringes, significantly improving patient safety (Figure 2).



Figure 2: Daikyo Crystal Zenith® 0.5 mL PFS.

Key Product Attributes

- **Advanced Construction:** Glass-like transparency with superior break resistance and dimensional accuracy, offering robust strength and safety for delicate ophthalmic procedures.
- **Silicone-Free Design:** Eliminates the risk of silicone-related particulates and protein aggregation, supporting stability of biologic formulations and improving injection consistency.
- **FluroTec Barrier Films:** Applied to both plunger and tip cap to reduce E&L, prevent drug-elastomer interaction and maintain long-term formulation integrity.
- **Low Particulates And Endotoxins:** Complies with USP <789> requirements for ophthalmic solutions, ensuring high optical clarity and patient protection.
- **Ready-To-Use Packaging:** Supplied sterile and compatible with nested tub configurations, allowing seamless integration into aseptic fill-finish operations.

The Daikyo CZ RU Luer lock syringe design with FluroTec film laminated D21-7HW chlorobutyl plungers provide smooth, controlled and consistent extrusion forces, ensuring predictable injection performance and a positive user experience across a range of delivery conditions. Additionally, the syringe exhibits exceptionally low particulate and endotoxin levels and meets USP <789> compliance for ophthalmic solutions, ensuring clarity, sterility and patient safety.

Overall, the Daikyo CZ RU Luer lock 0.5mL syringe represents a technologically advanced containment and delivery system that combines material innovation, precision engineering and proven performance to meet the evolving needs of complex biologics and ophthalmic formulations.

CONCLUSION

Ultra clean, low particulate PFS systems represent a critical convergence of advanced material science, heightened regulatory vigilance and tightly integrated supply chains. Innovations such as polymer-based barrels, low extractable elastomers and silicone-free or controlled lubrication designs can significantly reduce particulate risk and improve compatibility with sensitive biologics. At the same time, stringent global regulatory frameworks and enhanced inspection technologies are driving higher expectations for cleanliness, sterility and traceability. An integrated, end-to-end supply chain linking component manufacturing and distribution has become essential to consistently meet these quality demands while ensuring reliability, scalability and patient safety in modern injectable drug delivery.

West is in a unique position not only to provide PFS components, such as high-quality elastomeric plungers for PFS solutions, but also to offer a full polymeric PFS solution, such as the Daikyo CZ RU Luer lock 0.5 mL syringe. Furthermore, West's expertise extends beyond component supply to include analytical testing and technical support to help customers optimise system performance, mitigate risk and accelerate time to market. Through its global manufacturing footprint and

"STRINGENT GLOBAL REGULATORY FRAMEWORKS AND ENHANCED INSPECTION TECHNOLOGIES ARE DRIVING HIGHER EXPECTATIONS FOR CLEANLINESS, STERILITY AND TRACEABILITY."

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robust quality systems, West ensures consistent product integrity and regulatory compliance, empowering pharmaceutical partners to confidently deliver safe and effective ocular and other treatments to patients worldwide.

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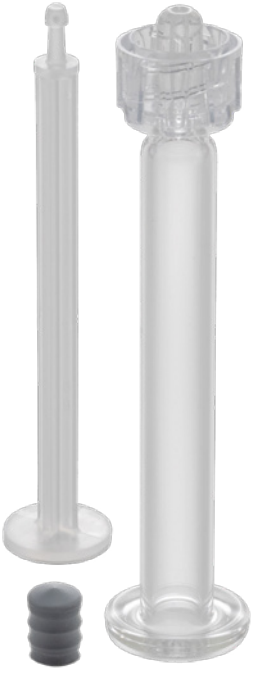
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THE CHALLENGES IN DEVELOPING AND MANUFACTURING CUSTOM OPHTHALMIC INJECTOR DEVICES

SANNER

Protecting Health.

Dr Lorna Barron of **Sanner** sets out the standards that must be met for effective drug delivery to the eye, characterising both old and new delivery routes that may be used to address the unique challenges of ophthalmic disease.

The global demand for ophthalmic drugs continues to rise, driven by aging populations,[1] increasing prevalence of chronic eye diseases and improved access to healthcare worldwide. Conditions such as age-related macular degeneration (AMD), diabetic retinopathy and glaucoma are being diagnosed earlier and treated more aggressively than ever before. As a result, pharmaceutical companies are investing heavily in new formulations and delivery methods to meet both clinical needs and patient expectations.

With the rapidly diversifying pipeline of ophthalmic treatments, including biologics, high-viscosity formulations, sustained-release systems and gene therapies, significant delivery challenges have arisen that legacy injector platforms are not designed to accommodate. Differences in viscosities, target injection volume, formulation properties and clinical workflow require tailored solutions. This need is reflected in market forecasts, with the global ophthalmic drug delivery device market projected to grow from approximately US$16.5 billion (£12.2 billion) in 2024 to $37 billion by 2033.[2]

"DIFFERENCES IN VISCOSITIES, TARGET INJECTION VOLUME, FORMULATION PROPERTIES AND CLINICAL WORKFLOW REQUIRE TAILORED SOLUTIONS."

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There are several targets for ophthalmic drug administration, including topical, intravitreal and subretinal. Each have their own challenges that require unique solutions (Table 1).

Route	Advantages	Disadvantages
Topical (eye drops)	Non-invasive, easy.	Low bioavailability due to corneal barrier and tear drainage.
Intravitreal injection	Direct delivery to back section of the eye (posterior segment).	Invasive. Risks such as infection. Clinician must administer. Frequent repeats mean high treatment burden.
Subretinal injection	Direct and localised target for retinal therapies. Appropriate for cell and gene therapies.	Invasive, requires complex procedure by highly skilled surgeon, risk of severe complications: retinal detachment, haemorrhage, etc.
Suprachoroidal injection	Targets posterior segment while limiting systemic exposure. Does not require full operating theatre.	Targeting of retina is less precise. Not as well established.

Table 1: Several different delivery routes for ophthalmic drugs, each with advantages and disadvantages.

TOPICAL DRUG DELIVERY

Topical drug delivery, most commonly via eye drops, remains the most widely used non-invasive approach for treating ocular conditions, yet its effectiveness is fundamentally constrained by ocular anatomy and physiology. Only a small fraction of an administered drop is retained on the ocular surface, as rapid tear turnover, reflexive blinking and limited tear volume lead to swift drug loss within minutes. In addition, drugs must traverse multiple corneal barriers with differing hydrophobicity and permeability characteristics, significantly limiting penetration and overall bioavailability. These factors often require frequent and higher dosing, increasing the risk of local and systemic side effects and contributing to poor patient adherence – particularly among elderly or physically limited populations.[3]

Researchers are actively developing new approaches to overcome these limitations, with key aims including increased residence time on the ocular surface, enhancement of tissue penetration and sustained drug release. Formulation innovations such as mucoadhesive polymers and *in situ* gelling systems can prolong contact with the precorneal environment and reduce rapid tear clearance. Additionally, advanced carrier systems including nanoparticles, liposomes and micelles can be used to improve corneal permeation and protect drugs from degradation. Finally, drug-eluting contact lenses and ocular inserts may provide sustained-release solutions without frequent dosing.

INTRAVITREAL INJECTIONS

Intravitreal injections are one of the most commonly performed ophthalmic procedures worldwide. These injections are typically administered in an outpatient clinical setting and involve the insertion of a needle through the sclera to inject directly into the vitreous humour, the gel-like substance that fills the central cavity of the eye. This delivery route allows drugs to bypass the barriers experienced by topical delivery and reach the posterior segment of the eye. Today, intravitreal injections of anti-vascular endothelial growth factor agents are an essential treatment for millions of patients with retinal vascular diseases, such as wet AMD and diabetic retinopathy.

Intravitreal injections, while clinically effective for delivering drugs to the posterior segment of the eye, also present several limitations and risks. They are inherently invasive, risking serious complications such as sight-threatening retinal detachment or endophthalmitis. Some procedures, such as intravitreal corticosteroid injections, can lead to increased intraocular pressure (IOP) due to increased outflow resistance of aqueous humour in the trabecular meshwork. Often, this acute effect may subside after injection; however, chronic IOP increases may occur with multiple injections, potentially leading to glaucoma over time. Many intravitreal drugs have relatively short half-lives, requiring repeat monthly or bimonthly injections. This high treatment burden places strain on patients, caregivers and healthcare systems and is associated with reduced adherence over time.[4]

Conventional syringe-based injections offer limited control over injection force, flow rate and drug distribution, which can be problematic regarding dosing variability, reflux at the injection site and cumulative ocular trauma. Sustained-release intravitreal implants and reservoir systems (such as port delivery systems) are being developed to reduce injection frequency and treatment burden, offering controlled long-term release while potentially lowering cumulative procedural risk and improving adherence.[5–7]

One such example is Contivue® a port delivery platform containing Susvimo®, a ranibizumab injection by Roche (Basel, Switzerland). This refillable intravitreal implant continuously delivers a customised formulation of ranivizumab over extended periods, significantly reducing the frequency of intravitreal injections required for chronic retinal diseases including neovascular (wet) AMD and diabetic retinopathy. This offers continuous delivery with just one refill every nine months for appropriate patients. The device is surgically implanted into the eye during a one-time outpatient procedure, with ancilliary devices used to fill, insert, refill and remove the implant.[8,9]

SUBRETINAL INJECTIONS

Subretinal injection delivers therapeutic agents directly into the space between the photoreceptors and retinal pigment epithelium, providing high-precision targeting of cells central to many retinal

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"THIS DIRECT DELIVERY FACILITATES HIGH LOCAL DRUG CONCENTRATIONS, RAPID UPTAKE BY TARGET CELLS AND MINIMAL SYSTEMIC EXPOSURE, MAKING IT ESPECIALLY VALUABLE FOR GENE AND CELL THERAPIES."

degenerative diseases, such as retinitis pigmentosa, AMD and inherited retinal disorders. This direct delivery facilitates high local drug concentrations, rapid uptake by target cells and minimal systemic exposure, making it especially valuable for gene and cell therapies where precise placement determines treatment efficacy. Moreover, the immune-privileged nature of the subretinal space can reduce immune reactions against viral vectors or transplanted cells compared with other routes.[10,11]

However, subretinal injections come with significant challenges. The procedure is highly technical and invasive, typically requiring a pars plana vitrectomy and creation of a subretinal bleb, which can itself pose risks for retinal tears, detachment, haemorrhage and cataract formation. Needle placement is difficult due to the tiny target space, and even small lateral movements can widen the retinotomy and promote reflux of the therapeutic agent into the vitreous, reducing delivery efficiency. Variability in injection speed and plunger movement can significantly influence the delivered volume and therapeutic effect, leading to dependence on the skill of the practitioner for manual devices such as standard intravitreal injection syringes. Additionally, the retinal cells may be subjected to high stress from a subretinal bleb that is created too quickly. Therefore, specialist surgical training and intraoperative imaging, such as optical coherence tomography (OCT), are required and robotic assistance is increasingly needed to improve precision and reduce variability.[12,13]

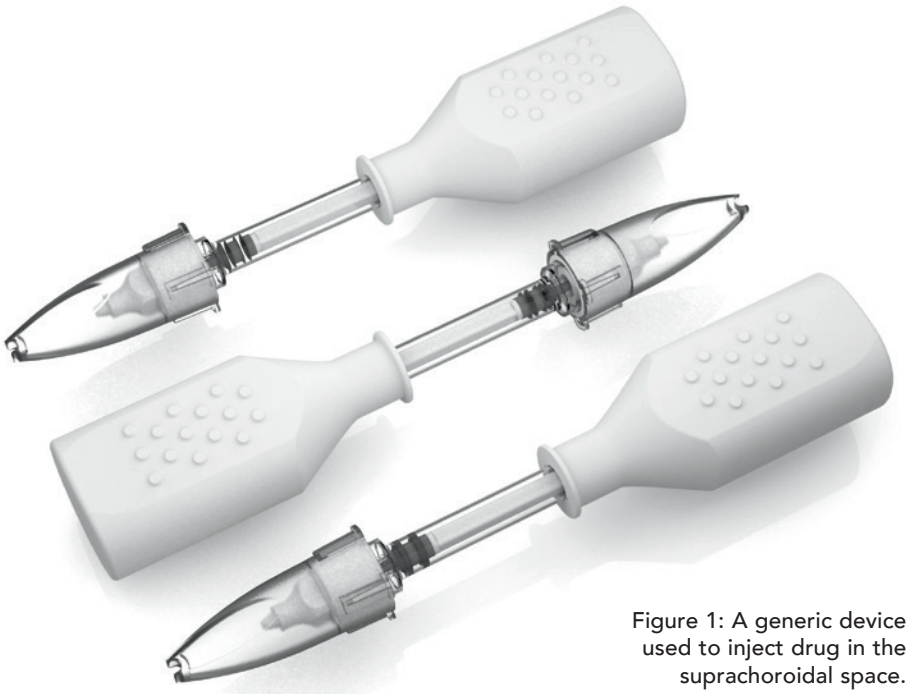


Figure 1: A generic device used to inject drug in the suprachoroidal space.

To address these challenges, researchers are exploring advanced techniques and devices, including ultra-fine cannulas, intraoperative OCT guidance and robot-assisted platforms, with the aim to standardise delivery, control injection depth and pressure, suppress tremors and reduce complications (Figure 1). These advances could make subretinal delivery both safer and more reproducible for gene, cell and other localised therapies.[11,14]

DEVICE DEVELOPMENT AND MANUFACTURING CHALLENGES

There is a clear need for delivery devices to go beyond conventional eye drop bottles and syringes. However, to translate emerging methods into the clinic, several important challenges must be overcome, including complex engineering needs, human factors and regulatory considerations.

Ophthalmic devices may require complex engineering to deliver new therapies. Formulations including carrier systems, such as nanoparticles or liposomes, may be sensitive to shear stress, requiring careful flow analysis of systems. Dosing accuracy on the microlitre scale is also essential, requiring control of mechanical tolerances, force feedback and fluid dynamics.

As the trend grows for high-viscosity biologics, there is a need for greater injection forces, which must be carefully controlled to ensure safe intraocular delivery. Additionally, sustained-release solutions, such as drug-eluting contact lenses or ocular inserts, must ensure predictable release kinetics.

Incorporating human factors into device development is also essential to reduce the risk of user error and to increase patient adherence. For topical applications, *in situ* gels, viscous formulations and mucoadhesives must be precisely dispensed in small, repeatable volumes without relying on patient technique. Devices must be intuitive, comfortable and suitable for elderly or physically limited patients, minimising the need for precise hand-eye co-ordination or frequent dosing.

Sanner conducts comprehensive human factors and usability studies to ensure that devices are designed around real-world users, environments and workflows. The company's studies evaluate critical user interactions, identify potential use-related risks early in development and inform design refinements that improve safety, usability and reliability. For more complex intraocular delivery, clinicians must be able to operate devices safely and consistently, and variation in clinicians' skill levels should not adversely affect the operation of the device. Through formative and summative human factors testing, Sanner helps to ensure that devices support consistent clinical performance, reduce training burden and meet regulatory expectations for usability and risk mitigation.

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Finally, regulatory requirements are a necessary part of device development. The eye is a vulnerable organ of the body, with injuries causing life-changing consequences. As these devices come into direct contact with ocular tissues, any contamination can cause adverse reactions ranging from irritation, infection or even vision impairment. Ophthalmic products and devices must therefore follow strict regulatory requirements. Different countries have various regulatory frameworks that account for factors such as packaging, sterilisation, quality control and adverse-event reporting. Additionally new ophthalmic devices often combine drug, device or biologic components, which must be designed with regulatory compliance in mind from the start. Robust safety and efficacy data are required before market approval can be obtained, with extensive documentation and validation. These hurdles can extend development timelines and increase R&D costs, especially for novel devices.

COMPUTATIONAL MODELLING AS A DEVICE DEVELOPMENT TOOL

Computational modelling is one tool that can be used to facilitate the design process. Computational fluid dynamics (CFD) modelling of both flow within an injector system and flow within the eye can provide insights such as shear stress applied to carrier systems, increases in intraocular pressure for different flow conditions or the injection forces required for different formulation viscosities. Release kinetics for different positioning or composition of ocular inserts can also be calculated using mass transport or multiphysics models to inform designs at an early stage.

The benefit of modelling techniques such as finite element analysis (FEA) and CFD is that they allow for efficient predictive testing of device performance under different designs and conditions. The impact of anatomical variation between patients on the biomechanics of the system can be examined by simple parameter changes in a model. This reduces the need for physical prototyping which, in turn, can shorten development timelines, lower costs and identify potential failure modes prior to clinical evaluation. Sanner has extensive experience in using multiphysics models to inform device design and facilitate optimised prototypes at an early stage of development.

"SANNER HAS EXTENSIVE EXPERIENCE IN USING MULTIPHYSICS MODELS TO INFORM DEVICE DESIGN AND FACILITATE OPTIMISED PROTOTYPES AT AN EARLY STAGE OF DEVELOPMENT."



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MANUFACTURING

Once a device design is finalised, manufacturing custom ophthalmic devices at scale introduces additional challenges. One challenge of manufacture is that ophthalmic devices target micro-scale anatomical features. Therefore, they often involve small components with tight tolerances and pristine surface finishes, which must maintain consistency across production lots. Sanner has deep expertise in precision injection moulding for pharmaceutical devices. Additionally, its new site in Germany offers cleanroom manufacturing, which is key to producing ophthalmic device parts.

Materials selection is also a major consideration, as the materials used for the device must be compatible with the drug formulation to ensure that aggregation, adsorption or degradation do not occur. Leaching of chemicals or particle generation from silicone oil coatings must also be avoided, and the device materials and drug formulation must also be able to withstand sterilisation. Wall thicknesses and aspect ratios may approach the limits of what can reasonably be manufactured for materials that meet all other requirements for a specific formulation.[15]

In addition, to be used for clinical drug use, sterile manufacturing must be carried out to meet regulations, pass quality control tests and maintain consistency throughout the entire manufacturing process. Depending on the device and formulation, the need for aseptic processing may arise. Terminal sterilisation of filled drug products is often the preferred approach of regulatory bodies; however, for many ophthalmic therapies, including cell and gene therapies, these sterilisation processes can cause degradation of the product. Sanner is a strong choice to help clients develop sterilisation concepts, and the company works closely with vetted external partners to achieve this.

Finally, scale-up of these processes can also be a challenge. Novel injection devices may rely on bespoke parts and materials that may have limited sources or long lead times. Careful planning is needed to reduce strain on the supply chain, as any delay in production may inflate costs.

Challenge	Capabilities	Example Application
Complex engineering tailored to new therapies	Computational modelling (e.g. CFD, FEA, multiphysics modelling) to optimise flow, injection forces, shear stress and release kinetics prior to prototyping.	Device design for delivery of a shear-sensitive high-viscosity nanoparticle suspension.
Microlitre-scale dosing accuracy	Precision engineering with tight mechanical tolerances, practical testing of forces and fluid dynamics analysis.	A subretinal injector that requires high dose accuracy.
Sustained-release systems	Computational modelling to predict release kinetics and optimise device positioning.	Drug-eluting contact lenses or ocular insert.
Human factors and patient adherence	Experienced human factors and industrial design team to design intuitive and effective device features.	Eye drop applicator with guided volume control for elderly patients.
Clinician variability for skilled procedures	Experienced human factors and industrial design team to develop ergonomic and fail-safe features for consistent use across skill levels.	A new microinjection device for suprachoroidal injections.
Materials selection	Experienced materials scientists can select the right combination for drug formulation, sterilisation, biocompatibility and manufacturing.	Coating for a drug-eluting ocular insert that maintains controlled release without leaching or degradation.
Precision manufacturing	Able to adapt plastic manufacturing processes to novel designs with tight tolerances.	Micro-moulded injector for an intraocular implant.
Sterilisation and aseptic processing	GMP-compliant facilities with cleanroom capabilities in the US.	Aseptic filling of eye ointment applicators.
Scale-up and supply chain	Use Sanner's global manufacturing network to ensure consistent supply, reduce lead times and co-ordinate bespoke parts.	Manufacturing of new ocular injection devices at commercial scale.
Reducing R&D cost and timeline	Integrated CDMO allowing for smooth transition from design to manufacture.	Smooth transition from prototype injector to GMP-manufactured ocular device.

Table 2: Novel device development challenges and capabilities to approach them.

"SUCCESSFULLY MOVING CUSTOM OPHTHALMIC INJECTORS FROM CONCEPT TO MARKET REQUIRES A PARTNER WITH DEEP EXPERTISE ACROSS DESIGN, DEVELOPMENT, REGULATORY PATHWAYS AND MANUFACTURING EXECUTION."

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CHOOSING THE RIGHT PARTNER

Due to the unique hurdles in development and manufacture of new ophthalmic injection devices, it is essential to choose a partner with the right experience. Successfully moving custom ophthalmic injectors from concept to market requires a partner with deep expertise across design, development, regulatory pathways and manufacturing execution (Table 2).

As an example, Sanner developed a fully customised injection device capable of delivering an extended-release pharmaceutical implant into the vitreous for the treatment of wet AMD and glaucoma (Figures 2 and 3). Drawing on the team's expertise, Sanner designed a custom needle assembly, including the hub, needle and cap, tailored to the client's needs. To support early research, Sanner then manufactured a small batch of over a thousand units, enabling critical toxicology testing and a human factors study with key opinion leaders.

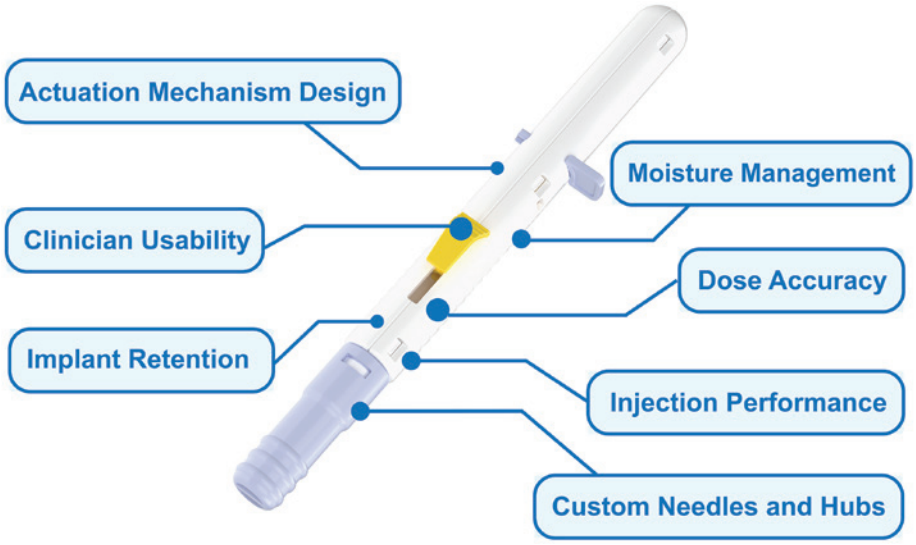


Figure 2: Breakdown of the ocular injection device developed by Sanner.



Figure 3: Ocular injection device developed by Sanner for the treatment of wet AMD and glaucoma.



Figure 4: Sanner has over 15 years' experience in manufacturing pipettes for eye drops under cleanroom conditions.

Sanner's specialised expertise in ophthalmic injection device development supports ocular therapeutics programmes from preclinical stages through to commercialisation. Its team brings experience in designing devices that use a range of active ingredients, including hydrogels. With proven know-how in bringing ophthalmic injectors to market, Sanner serves as a reliable device partner throughout a product's journey to market success.

Sanner brings decades of experience in medical device engineering, precision manufacturing and pharmaceutical injection moulding in cleanroom environments (Figure 4). With the right capabilities, Sanner helps customers overcome the many challenges inherent in ophthalmic injector development – accelerating time to market while ensuring safety, performance and regulatory compliance.

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Dr Tina Rogers of WuXi AppTec discusses antibody-drug conjugates and their potential in direct targeting and treatment of cancers, going further to assess the risks of these treatments and how they can be mitigated.

"OVER TIME, THE STABILITY, EFFECTIVENESS AND SAFETY OF ADCs HAVE BEEN SIGNIFICANTLY IMPROVED BY ADVANCEMENTS IN ANTIBODY ENGINEERING, BIOLOGICAL CONJUGATION TECHNOLOGY, LINKER TECHNOLOGY AND OTHER RELATED BREAKTHROUGHS."

Antibody-drug conjugates (ADCs) are among the most promising drugs in the fight against cancer, owing to their unique design and unmatched precision. However, they present ocular safety challenges that can derail development if not addressed, leading to costly delays or regulatory setbacks.

Ocular toxicity can cause a wide range of issues for patients, including blurred vision, night blindness, inflammation of the cornea and other problems of varying severity and incidence. These adverse effects can limit the therapeutic use of ADCs and necessitate close monitoring and management during treatment.

With the appropriate development approach, sponsors can either avoid or mitigate these issues, ensuring that this powerful class of drug is as impactful as possible and reaches the patients who need it most, safely and efficiently.

HOW ADCs WORK

ADCs are designed to selectively deliver a payload, commonly referred to as a "warhead", directly to a target – typically cancer cells – improving treatment efficacy while reducing systemic exposure and off-target effects. An ADC can achieve this because it consists of three main parts: a monoclonal antibody (mAb) with specificity for a tumour cell surface protein, a payload and a linker that connects the first two elements. After the mAb binds to the target, the linker is biochemically cleaved or spontaneously degrades, releasing the payload at a sufficient concentration to act on its target, while the receptor-ADC complex is internalised via endocytosis.

ADCs were first introduced in 1900 by Nobel laureate Paul Ehrlich, who envisioned

"ADCs ARE AMONG THE MOST PROMISING DRUGS IN THE FIGHT AGAINST CANCER, OWING TO THEIR UNIQUE DESIGN AND UNMATCHED PRECISION."

that these drugs could selectively target tumour cells while sparing healthy ones, hence the "magic bullet" term he gave them. Early experimental ADCs emerged in the 1980s and 1990s, but the field reached its first major milestone in 2000, when gemtuzumab ozogamicin was the first ADC approved for clinical use, validating the concept.[1] However, early practices also highlighted safety and design challenges. After the drug reached patients, adverse effects and early mortality resulted in regulators pulling it from the market, later allowing it back at a lower dose given in split portions.

This experience made clear what needed resolving going forwards – the chemical "linker" that holds the drug together must stay intact in the bloodstream and only release inside cancer cells, so that the toxic warhead cannot spill into healthy tissue. Developers must choose the right tumour target and fine-tune how much drug to give and how often. Over time, the stability, efficacy and safety of ADCs have been significantly improved by advancements in antibody engineering, biological conjugation technology, linker technology and other related breakthroughs.

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Of the 19 ADCs approved for use as of mid-2025,[2] all are for the treatment of cancers, including lymphoma, specific cases of leukaemia, relapsed or refractory multiple myeloma, and metastatic triple-negative and HER2-positive breast cancer. Future drugs may also treat other conditions, including autoimmune and inflammatory diseases. However, the diverse spectrum of adverse effects in ADCs must be considered in order to prevent delays or discontinuation of treatment, which can adversely affect patient outcomes. This makes the management of off-target effects crucial to maximising efficacy and the number of future applications of ADCs.

THE ADVERSE EFFECTS OF ADCs

Even with all their promise, ADCs by nature are also associated with a number of adverse effects and toxicities, including haematologic side effects such as neuropathy, lymphopenia, neutropenia, thrombocytopenia and more. Payload-specific toxicities and adverse effects may vary based on the drug type and target. Sponsors of ADC drugs should monitor for these conditions during the development and testing process to identify appropriate uses, dosing and labelling. Some examples of ADCs that have toxicity issues include:

- **Monomethyl Auristatin E (MMAE):** ADCs using this payload often cause anaemia, neutropenia, and peripheral neuropathy.
- **Drug Maytansinoid 1 (DM1):** These ADCs are linked to thrombocytopenia and hepatic toxicity.
- **Pyrrolobenzodiazepine (PBD):** Can cause severe myelosuppression, prolonged cytopenias, hepatotoxicity and delayed organ toxicity.
- **Monomethyl Auristatin F (MMAF) and DM4:** Frequently associated with ocular toxicity.

THE EFFECTS OF OCULAR TOXICITY

Ocular toxicities are among the most clinically impactful toxicities for many ADCs and control of these requires early planning and active monitoring during ADC therapy. These toxicities often affect the cornea or ocular surface and manifest as a foreign-body sensation and blurred vision. They may also present with clinical symptoms such as corneal fluorescein staining, pseudomicrocysts and conjunctivitis.

> "STRATEGIES TO REDUCE OFF-TARGET UPTAKE ARE EMERGING AND PRESENT A POTENTIAL PATH TO HELP REDUCE OCULAR TOXICITY."

This is most common in ADCs such as enfortumab vedotin and tisotumab vedotin, which have been linked to high incidences of ocular toxicity in clinical trials. Enfortumab vedotin carries a warning for ocular disorders as the incidence of ocular toxicities with the drug can reach as high as 46%, with dry eye the most commonly reported symptom, affecting 36% of patients.[3]

The pathogenesis of ADC-related ocular adverse effects has been attributed to the unique molecular structure of the drug type, the cytotoxic mechanism of its payload and the expression of target antigens on both tumour and healthy ocular cells. However, the precise mechanisms that cause these effects remain elusive to researchers.

Despite this, it is thought that ADCs cause ocular-related adverse effects through both on-target and off-target mechanisms. On-target toxicity can occur when the target antigen of ADCs is also present on healthy eye cells. For example, HER2 is expressed on corneal epithelial cells, allowing HER2-targeting ADCs, such as trastuzumab emtansine or trastuzumab duocarmazine, to be taken up by these cells, causing damage. In contrast, off-target toxicity arises from non-specific uptake of ADCs or their payloads by normal cells, even when the target antigen is absent. An example is belantamab mafodotin, where ocular toxicity occurs despite the absence of target-dependent uptake.

Growing evidence in this area suggests that most ADC-related ocular adverse effects are target-independent and driven primarily by the payload, rather than by antigen expression on normal eye tissue. As a result, strategies to reduce off-target uptake are emerging and present a potential path to help reduce ocular toxicity.

PRECLINICAL TESTING AND STUDY DESIGN FOR MITIGATION OF OCULAR TOXICITY

To meet the safety demands of emerging modalities such as ADCs, toxicology must become more adaptive and integrative, with safety assessments embedded earlier in the development lifecycle. This will allow predictive tools to guide candidate selection and study design. Developers must carefully select the target, antibody, cytotoxic payload and linker to ensure that an ADC realises its therapeutic potential while maintaining safety standards and reducing adverse effects such as ocular toxicity. They must also account for the nuanced characteristics and risks that are not always captured by conventional preclinical assays.

One of the primary and unique concerns in ADC testing is variability in the drug-to-antibody ratio (DAR), which can significantly affect a drug candidate's efficacy, safety and pharmacokinetics. The DAR determines the amount of drug delivered, the duration of ADC circulation and safety. The goal of researchers is not to achieve the highest DAR, but to achieve the appropriate ratio, balancing efficacy, PK and safety. Advanced bioanalytical methods can precisely quantify free and conjugated payloads, as well as antibodies, to characterise the PK profile.

Another crucial step in developing this new modality is determining the maximum tolerated dose (MTD) of each compound.

> "ADVANCED BIOANALYTICAL METHODS CAN PRECISELY QUANTIFY FREE AND CONJUGATED PAYLOADS, AS WELL AS ANTIBODIES, TO CHARACTERISE THE PK PROFILE."

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It is essential to set an appropriate preclinical threshold to inform dose selection and risk mitigation strategies. MTD testing can help to establish safety parameters in order to advance therapies into clinical trials and ensure that developers are better equipped to address the intricate balance between safety and efficacy.

BEST PRACTICES FOR OCULAR TESTING IN ADC DEVELOPMENT

Many ADC-related ocular toxicities can be identified and reduced before clinical trials begin by intentionally building eye safety into early development. This includes assessing whether the target antigen is present in healthy eye tissue, testing ADCs and their payloads on human eye-surface cells to determine whether toxicity occurs in the absence of target expression, and examining how the drug enters cells via non-specific uptake.

Developers can also reduce ocular risks by modifying ADC design by, for example, improving linker stability, lowering drug load or reducing hydrophobicity. Furthermore, they can closely study eyes during animal studies using appropriate ophthalmic exams. Together, these steps can help to predict ocular risks early and guide safer dosing, monitoring or redesign decisions prior to human exposure.

Once an ADC drug reaches clinical trials, optimising the dose and treatment schedule can further improve ADC safety. Dose capping, fractionated administration and limiting treatment duration can generally reduce toxicity, while prophylaxis for patients at high risk can further mitigate adverse effects.

NAVIGATING REGULATORY GUIDELINES

A careful and proactive approach to monitoring and mitigating ocular toxicity risks also aligns with global regulatory guidelines. By integrating this approach early in the process, drug sponsors can demonstrate that the risk is anticipated, understood and managed, rather than being unexpected. This means leveraging a preclinical pathway that explains a likely mechanism, linking it to a defined monitoring plan and specifying in advance how dose interruptions, reductions or discontinuations will be handled if toxicity occurs.

Starting early in trials, using established assessment tools, documenting mitigation

"BY INTEGRATING THIS APPROACH EARLY IN THE PROCESS, DRUG SPONSORS CAN DEMONSTRATE THAT THE RISK IS ANTICIPATED, UNDERSTOOD AND MANAGED, RATHER THAN BEING UNEXPECTED."

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measures and being transparent about severity and reversibility all help to build regulatory confidence. It is also crucial to align teams early on, ensuring that there is no miscommunication among those working on each stage of the regulatory process. Ultimately, regulators are not seeking to eliminate risk completely, they just want to ensure that it is predictable, measurable and controllable.

EFFECTIVE OCULAR ASSESSMENTS

Due to the high incidence of adverse effects, consistent monitoring is required at the clinical stage and beyond. Diagnosing ocular toxicity in ADCs involves a thorough cadence of clinical assessment, imaging and functional testing throughout the treatment period. Slit-lamp biomicroscopy is recommended to establish a baseline in a patient. This baseline should capture any pre-existing dry eye, corneal disease, cataracts, glaucoma and contact lens use, as these factors can confound disease grading and management.

Once in the clinic, a few key tests performed regularly are critical for the efficient and responsible monitoring of side effects and ocular toxicity. Fluorescein and lissamine green staining are used to identify corneal and conjunctival epithelial damage, and corneal confocal microscopy provides high-resolution imaging of microcysts and nerve alterations. Schirmer's Test and tear breakup time can help to evaluate any ADC-induced dry eye. Finally, optical coherence tomography can detect changes in the corneal and retinal structure. Early diagnosis of ocular issues enables dose adjustments, temporary treatment interruptions and other strategies to manage ocular toxicity.

A FINAL WORD ON ADC-RELATED OCULAR TOXICITY

ADCs are one of the most popular drug modalities being developed in the world today. They hold considerable potential for treating cancers and could make a significant difference to countless lives. However, adverse effects – ocular toxicity in particular – may dampen their impact or cause avoidable issues that impact health and quality of life. Even when adverse effects are mild, they can derail treatments and reduce their effectiveness.

For the many sponsors working in this area, ocular safety should be considered at the forefront of the development process and should continue beyond the point at which drugs reach patients. This can ensure that ADCs are delivered to market in the most efficient and safe manner possible, while adhering to regulatory standards.

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WuXi AppTec is a partner and contributor to the pharmaceutical and life sciences industries, providing R&D and manufacturing services that help advance healthcare innovation. With operations across Asia, Europe and North America, WuXi AppTec offers integrated, end-to-end services through their unique CRDMO platform. WuXi AppTec works alongside nearly 6,000 partners across over 30 countries, supporting their efforts to bring breakthrough treatments to patients. Guided by a vision that every drug can be made and every disease can be treated, they are committed to advancing breakthroughs for patients – one collaboration at a time.

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