OPHTHALMIC DRUG DELIVERY

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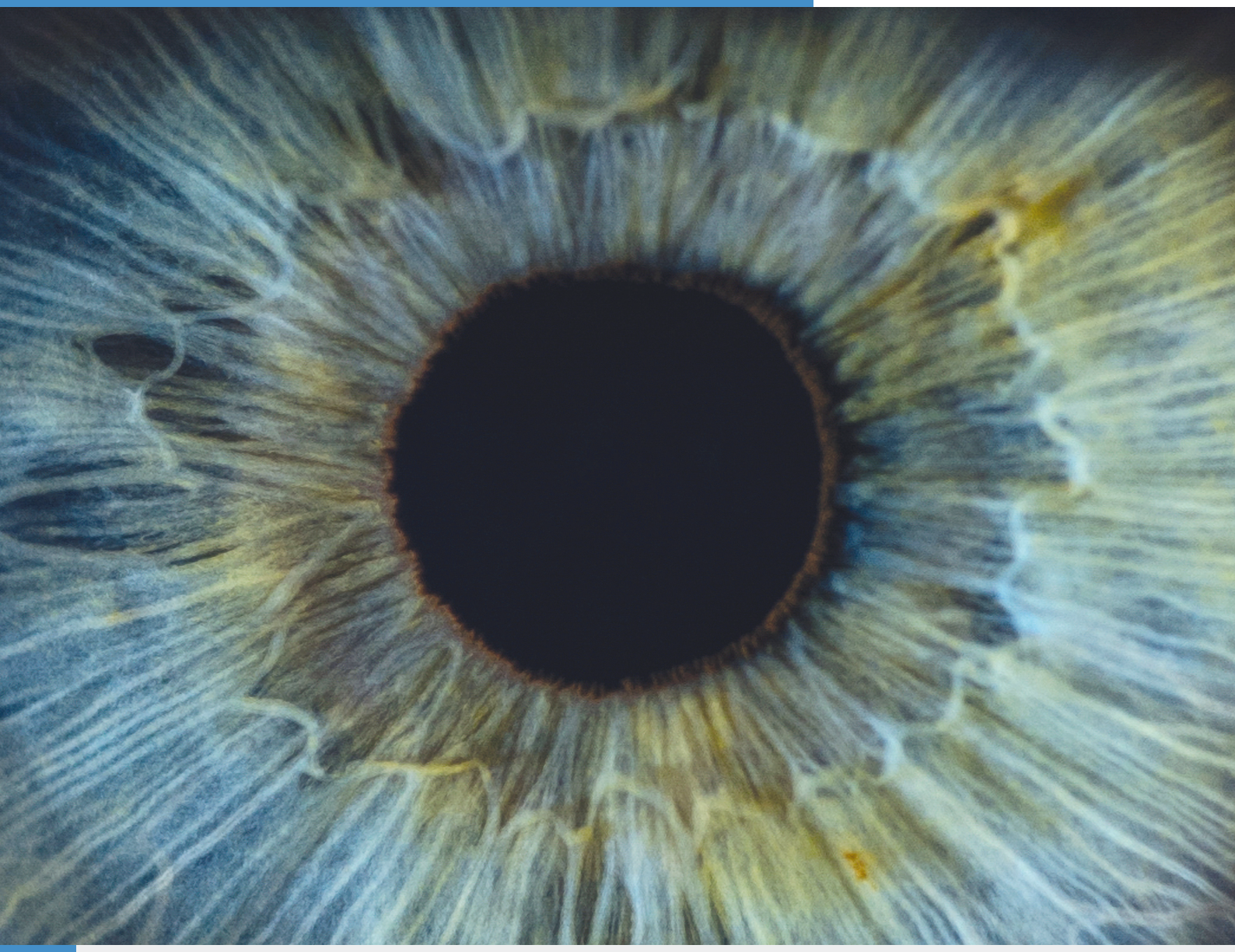

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Contents

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OPHTHALMIC DRUG DELIVERY

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EDITORIAL CALENDAR

Apr/May 2021	Pulmonary & Nasal Drug Delivery
May	Injectable Drug Delivery
Jun	Connecting Drug Delivery
Jul	Novel Oral Delivery Systems
Aug	Industrialising Drug Delivery
Sep	Wearable Injectors
Sep/Oct	Drug Delivery & Environmental Sustainability
Oct	Prefilled Syringes & Injection Devices
Nov	Pulmonary & Nasal Drug Delivery
Dec	Connecting Drug Delivery
Jan 2022	Skin Drug Delivery: Dermal, Transdermal & Microneedles
Feb	Prefilled Syringes & Injection Devices
Mar	Ophthalmic Drug Delivery
Mar/Apr	Drug Delivery & Environmental Sustainability
Apr	Pulmonary & Nasal Drug Delivery

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CONSIDERATIONS FOR OPHTHALMIC DRUG DELIVERY AND DEVELOPMENT

In this article, Robert Lee, PhD, President of the CDMO Division of Lubrizol Life Science Health, discusses recent advances in ophthalmic dosage forms and how companies are meeting these challenges to better serve their customers.

There has been a rise in the incidence of ocular conditions due to an ageing population, an increase in diabetes and other diseases, and improved diagnoses of many serious eye disorders. Companies have been discovering innovative drugs to treat these conditions, but the development of effective ophthalmic formulations can be challenging. These obstacles arise from the increasingly common bioavailability and solubility issues with new drugs, as well as stability, sterility and patient concerns.

> "While topicals are the most popular dosage form on the market for the treatment of eye conditions, there is a growing need for injectables and implantables for some serious, hard-to-treat ophthalmic conditions."

OPHTHALMIC DOSAGE FORMS

While topicals are the most popular dosage form on the market for the treatment of eye conditions, there is a growing need for injectables and implantables for some serious, hard-to-treat ophthalmic conditions. The main dosage forms include the following:

- Topicals, which can be delivered as eye drops (emulsions, suspensions or solutions), gels or ointments. A common example is Restasis® (Allergan, Dublin, Ireland), a topical ophthalmic emulsion for the treatment of dry eye.
- Injectables often come in two forms:
  - Periocular (administered to tissue closely surrounding the eye)
  - Intravitreal (injected into the fluid within the eye). Notable developments in the past several years include Regeneron's Eylea® (aflibercept) and Roche's Lucentis® (ranibizumab), both of which are biologics
- Implants and inserts, which can be bioabsorbable or non-bioabsorbable and can be used to release drug for up to several years. They can be injected, surgically inserted or placed beneath the eyelid or in the lacrimal punctum. For example, Allergan's Ozurdex® (dexamethasone intravitreal implant) is implanted in the retina to treat macular oedema.

INDUSTRY TRENDS

The ocular market is continually growing – an eight-fold increase was seen in the number of NDAs and biologics license applications (BLAs) between 2015 and 2018.

The market is also increasingly focused on select disease states, primarily:

- Dry eye
- Post-op pain and inflammation following cataract surgery
- Glaucoma
- Diabetic retinopathy
- Wet and dry age-related macular degeneration.

Among the treatments available for these disease states, retinal disorder therapies, such as biologics and gene therapies, have contributed to much of the market growth. These therapies are trending toward longer-acting products, such as intravitreal injections, especially with poly(lactic-co-glycolic acid) (PLGA) microparticles. Additional trends include formulations with multiple APIs, improved delivery devices for topicals, and preservative-free options such as sterile multidose eye-drop bottles.

ANTERIOR AND POSTERIOR DRUG DELIVERY

The administration site of ocular drugs can be divided into two categories, anterior and

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"Poor aqueous solubility can be viewed as an opportunity for innovation, as there are multiple methods that can be used to increase drug solubility or dissolution rate and, therefore, bioavailability."

posterior drug delivery. Anterior delivery, or "front" of the eye, includes the surface of the eye and primarily involves penetrating the cornea. Posterior delivery, or "back" of the eye, mainly targets the retina.

Topical drug administration to the front of the eye has been the standard of care for the treatment of ocular diseases for decades. However, low drug penetration – usually less than 5% of a drug is absorbed[1] – limits the effectiveness of topical treatments. Additionally, topical therapies cannot be used to treat back-of-the-eye disorders; the necessary diffusion distance to the site of action and the viscosity of the vitreous render topicals ineffective. As a result, the posterior segment of the eye is typically the most difficult area to treat, and ocular injections and implants are the only viable treatment options.[2]

In addition to eye anatomy, other considerations for effective ocular treatments include:

- Solubility and bioavailability issues with APIs
- API and product stability
- Product sterility
- Packaging and product containment needs.

ENHANCING BIOAVAILABILITY

Low aqueous solubility and poor stability of many APIs mean that 70–90% of new drugs suffer from bioavailability issues.[3,4]

However, with the right development partner, this does not have to be a deal-breaker. Indeed poor aqueous solubility can be viewed as an opportunity for innovation, as there are multiple methods that can be used to increase drug solubility or dissolution rate and, therefore, bioavailability.

One solution to this issue is to choose the correct drug delivery technology. Below are a few options drawn from our experience.

NANOPARTICLES

One method is particle size reduction, mainly with nanoparticulates, which increases the surface area of the drug particles and enhances the rate of dissolution. There are many nanoparticulate systems, which work in a variety of dosage forms:

- Pure API
- Solid lipid nanoparticles (SLNs) with API contained in a lipidic matrix
- Polymeric nanoparticles, which are similar to SLNs but with a polymer *in lieu* of lipids
- Nanocapsule systems, such as:
  - Liposomes, which are comprised of an aqueous core and a lipid bilayer shell
  - Emulsions, which are an oil core with a surfactant shell.

Below, we discuss in more detail some of these nanoparticle systems.

Solid lipid nanoparticles

SLNs are comprised of a solid matrix core that can solubilise lipophilic compounds, which are then dispersed and stabilised by an emulsifier. They improve stability and can protect a drug from chemical degradation. These systems can be used for a wide variety of APIs. Some SLNs can be terminally sterilised – which is a great benefit – although this does not apply to biologics.

Liposomes

Liposomes are constructed to deliver a drug inside a phospholipid bilayer, which is naturally attracted to cell membranes and facilitates effective drug transfer. These systems can deliver both hydrophobic drugs, dissolved in the bilayer, and hydrophilic drugs, dissolved in the aqueous core. This is a viable option for oligonucleotides used in gene therapies, which are on the rise in ophthalmics.

Liposomes can also improve biodistribution of a drug *in vivo* by mimicking cells; they are good at containing potent APIs (e.g. steroids); and are suitable for topical, sprayable and injectable systems.

MICROPARTICLES

Microparticle systems are an option for improving stability by protecting an API from enzymatic degradation in the body. They offer controlled and sustained release and can be used in topicals to aid muco-adhesion or as injectable depots.

For biodegradable systems, PLGA is the most common polymer used to encapsulate a drug due to its ability to break down safely in the body and release drug at a controlled rate.

IMPROVING END-PRODUCT STABILITY

Many APIs are sensitive to environmental conditions such as light, humidity, temperature and pH, which can affect product shelf life and stability. Shelf life refers to changes in the physicochemical properties of a drug product in its primary packaging when under typical storage conditions. Long-term storage conditions and the materials used in bottles and vials can greatly impact stability, for example, semipermeable ophthalmic bottles need to be stored at lower humidity conditions.

The stability of a drug product is also affected when introduced to a biological system. Many ocular drugs are subject to enzymatic and hydrolytic stresses present on the surface of the eye or within the vitreous, resulting in a shorter half-life.

Stability can be improved with several methods, including cold storage and lyophilisation. Refrigeration is required for most ophthalmics, especially for temperature-sensitive biologics. Nearly all intravitreal injections on the market are stored at refrigerated temperatures (2–8°C).

Lyophilisation, or freeze-drying, is used to preserve or stabilise materials and can be done aseptically. It may also preserve the integrity of water-sensitive products.

THE NEED FOR STERILITY

As with any parental product, sterility is a critical quality attribute of all ophthalmics as the human eye is highly susceptible to bacteria and irritants. The US FDA has issued many warnings concerning sterility over the years to some developers and contract development manufacturing organisations (CDMOs) manufacturing ophthalmics, creating a clear demand for partners that can provide sterile, expertly run facilities.

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The two methods of sterilising drug products are terminal sterilisation and aseptic processing. Terminal sterilisation involves filling and sealing a product under high-quality environmental conditions, then sterilising the final product in its primary container using:

- Heat
- Radiation (gamma rays, e-beam)
- Sterile filtration followed by aseptic fill-finish
- Ethylene oxide gas.

Terminal sterilisation is the preferred method, but the complex components increasingly found in ocular drugs, such as biologics and nanoparticles, cannot always tolerate this process. The FDA requires aseptic processing to be used only when terminal sterilisation is not possible.

Aseptic processing involves a drug product and its container being sterilised separately then brought together as a finished product under sterile conditions. This may require sterilising excipients and API separately.

The formulator must be careful with the selection of the sterilisation methods as this can affect the physicochemical properties (e.g. the stability and viscosity) of the final drug product. It is imperative to find a partner with a lot of experience of sterilisation, along with a proper facility and equipment for the required drug delivery methods.

CONTAINMENT

Many ocular drugs on the market and in development are highly potent compounds and need to be handled appropriately to protect employees and customers, adding complexity to the development process. This often includes corticosteroids and biologics (e.g. vascular endothelial growth factor [VEGF] inhibitors), two common API types in ophthalmics. Containment efforts may include:

- Isolator technology, in which the negative pressure differential minimises the potential for contamination
- Cleanrooms that maintain negative pressure compared with adjacent areas
- Facility-wide high efficiency particulate air (HEPA) filtration of incoming air and exhaust.

PACKAGING

Depending on the dosage form, ensure your development partner can fill your bottle, vial or tube at the proper volume and batch size. Injectables can be filled into vials, ampoules or prefilled syringes. Topicals can use single-use droppers, such as a blow-fill-seal, or a multidose bottle.

For topicals, the market is increasingly moving away from preservatives in formulations due to potential irritation and toxicity.[5] However, it can be challenging to dose ophthalmics sterilely when the bottle holds multiple doses and the seal is broken during initial use. Many innovations have emerged as a result, including sterile multidose bottles made by Aptar Pharma (IL, US), Nemera (La Verpillière, France) and Aero Pump (Hochheim am Main, Germany), among others.

For injectables, many formulations traditionally filled into vials are now being considered for prefilled syringes. Prefilled syringes have significant advantages, such as simplified, more convenient drug administration, reduced likelihood of improper dosing and less opportunity for contamination. Considerations when determining good candidates for prefilled syringes include whether your manufacturer has the proper capabilities, glass versus plastic syringe, precipitation of the drug product and the potential for modified degradation induced by adsorption and/or absorption of API or excipients by the syringe.

CONCLUSION

Special considerations must be taken when developing and manufacturing ocular drugs to ensure that treatments are safe, sterile and effective.

As the industry moves towards more complex APIs, dosage forms and delivery vehicles, those who do not have the capabilities to develop or manufacture an ocular product in-house should evaluate partners skilled in a wide variety of applications and highly adaptive to the evolving market.

Ophthalmics consistently encounter bioavailability, solubility and stability issues, while patient compliance and sterility should also be considered when developing new products. Developers should not be discouraged by these challenges, however, as success is possible with the right partner.

> "Many ocular drugs on the market and in development are highly potent compounds and need to be handled appropriately to protect employees and customers, adding complexity to the development process."

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Robert Lee, PhD, President, Lubrizol Life Science Health, CDMO Division, is responsible for product and business development along with providing strategic direction. Before joining Lubrizol, Dr Lee held senior management positions at Novavax, Lyotropic Therapeutics and Imcor Pharmaceutical Co. He holds BS degrees in Biology and Chemistry from the University of Washington, US, and a PhD in Physical Bioorganic Chemistry from the University of California, Santa Barbara, US. Dr Lee has published more than three dozen articles and five book chapters, as well as holding 11 issued patents and 15 provisional or PCT patent applications. He has over 30 years of experience in pharmaceutical research and development of both therapeutic drugs and diagnostic imaging agents. Dr Lee maintains strong academic ties, including an appointment as Adjunct Associate Professor of Pharmaceutical Chemistry at the University of Kansas, US, in the early 1990s, serving as a reviewer for both the International Journal of Pharmaceutics and Journal of Pharmaceutical Sciences, and serving on the Editorial Board for the Journal MOJ Bioequivalence & Bioavailability, The Scientific Pages of Nanotechnology and the Journal of Analytical and Pharmaceutical Research.

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STATE-OF-THE-ART SOLUTIONS FOR OPHTHALMIC STERILE DRUG PRODUCT MANUFACTURING

In this article, the first in a series of two, Rainer Glöckler, Chief Technical Officer, and Carole Delauney, Director Business Development, both of Swissfillon, discuss how the company's state-of-the-art filling line meets the requirements and complexities that are particular to ophthalmic drug product manufacturing. The second article, to be published in May, will explore partnerships between pharma, CDMOs and syringe manufacturers in more detail.

Advanced drug products (DPs) filled in innovative containers, with small to mid-size annual demand (fewer than 500,000 units) pose a major challenge to existing manufacturing business models based on large throughputs. Ophthalmic DPs, which often fit into this advanced DP category, additionally require a high level of process knowhow and state-of-the-art manufacturing technologies in order to maximise safety, meet stringent regulatory requirements and minimise costs.

Here we will show how Swissfillon's aseptic manufacturing services, and its innovative, fully automated, highly flexible filling line at its facility in Visp, Switzerland (Figure 1), are perfectly positioned to fulfill the requirements of this market segment.

OVERVIEW OF THE OPHTHALMIC MARKET FOR RETINAL DISORDERS

Retinal disorders include diabetic retinopathy and age-related macular degeneration. They are caused partly by over-production of a protein called vascular endothelial growth factor (VEGF), and are treated with anti-VEGF drugs, which can be administered by intravitreal injection into the back of the eye using prefilled syringes. These require the highest quality primary packaging and DP manufacturing (filling) technologies which ensure maximum safety, meet regulatory requirements and minimise overfill of the syringes.

The global ophthalmic drug market is forecasted to grow from US$28.4 billion

Figure 1: Swissfillon's facility in Visp, Switzerland.

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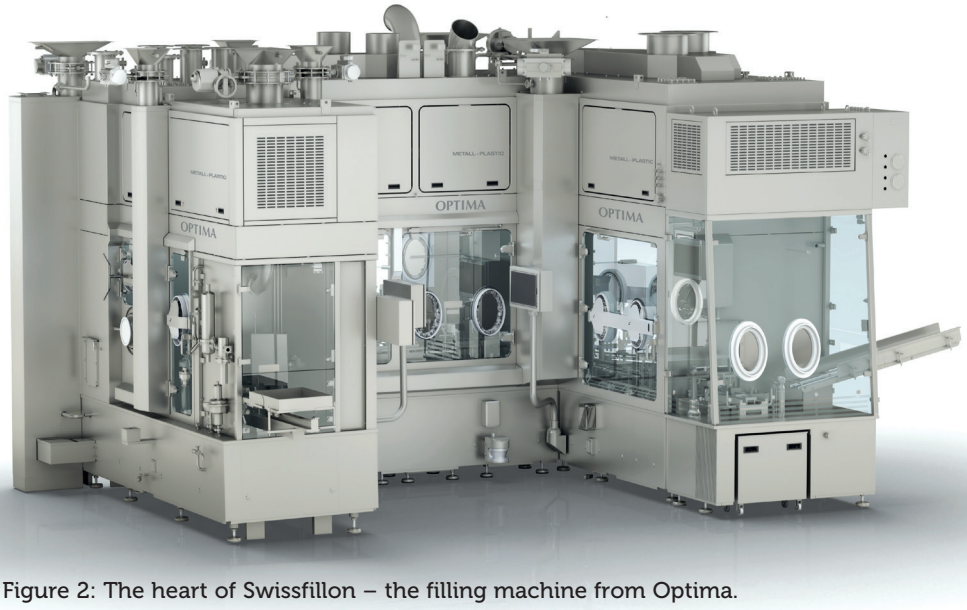

Figure 2: The heart of Swissfillon – the filling machine from Optima.

"At the Phase II clinical stage, as the product becomes more mature, there is often a switch from vials to prefilled syringes."

(£20.1 billion) in 2020 to $36.2 billion in 2025, and to reach $47.6 billion by 2030. In 2020, retinal disorder drugs accounted for the largest share of the market, with sales of $13.1 billion and 46% market share.[1] Growth in the market will be driven by the rapidly ageing global population, the increasing prevalence of diabetes leading to ocular diseases, unmet clinical needs in many disease areas, and economic growth resulting in increased demand in developing countries, particularly in Asia.

The opening up of the market to biosimilar drugs as the patents of blockbuster drugs expire over the next few years represents a major opportunity for new players wishing to enter the sector, and pharma companies are working on next-generation ophthalmic formulations. The R&D pipeline for drugs to treat retinal disorders is very strong, with new classes of therapeutic agents and innovative formulations being developed by biopharma companies.

SPECIFIC REQUIREMENTS AND COMPLEXITY IN OPHTHALMIC DP MANUFACTURING

In most cases, the vial is the preferred choice for primary packaging at the development stage. At the Phase II clinical stage, as the product becomes more mature, there is often a switch from vials to prefilled syringes. For some indications, including ophthalmics, vials are preferred for some specific markets, and therefore they remain a focus until the DP reaches the market.

Key considerations for ophthalmic primary packaging and DP manufacturing are set out below.

Manufacture Vials and Prefilled Syringes for the Same DP

The Optima multipurpose filling line qualified at Swissfillon (Figure 2) offers the flexibility for customers to fill both vials and syringes during the full cycle of their product launch on the same machine. As long as the packaging is already implemented on Swissfillon's system and the starting material is available, the customer can place a purchase order for filling vials or prefilled syringes and can readily switch from one to the other. Swissfillon has very good relationships with the main primary packaging suppliers offering ophthalmic solutions, which leads to improved and timely solutions for customers.

Meeting Regulatory Requirements on Subvisible Particles and Avoiding "Floaters"

Ophthalmic drugs should essentially be free of visible and subvisible particles. These can occur due to contamination or may arise from primary packaging or during the filling process. There is evidence that silicone oil plays a role in both the denaturation of proteins and the initiation of aggregation processes in proteins.[2] USP <789> relates to visible and subvisible particles, and there are specific guidelines for clinical ophthalmic applications. Even if the subvisible particle requirement is met, "floaters" may occur. These are a kind of a micro silicone oil droplet which remains in the eye.[3]

Ensuring Accuracy at Low Volumes

The range of the fill volume is usually 100–200 µL. Swissfillon's speciality is that its filling line transports through vial by vial or syringe by syringe on the same machine. This allows every container to be weighed using the tare and gross weigh installed on the machine, so it can calculate how much volume there is in each container, and a feedback loop corrects the pump automatically.

"Swissfillon's speciality is that its filling line transports through vial by vial or syringe by syringe on the same machine."

This approach means it can achieve exceptionally precise filling. Despite such low fill volumes, Swissfillon guarantees an accuracy of ±5%, and typically achieves an accuracy well within ±2%. Also, any underfill or overfill results in just a single syringe being rejected, compared with nest filling where inaccurate filling would usually result in 10 to 50 syringes being rejected. If required, Swissfillon is able to perform filling activities for ophthalmic drugs using a rotary piston pump, which precludes the possibility of particulates occurring due to damage to the pump tubing.

Minimising Overfill for Drug Substance Cost Savings

Containers are typically overfilled by a factor of three in order to guarantee the safe expected extractable volume, either directly injected from the prefilled syringe or extracted from a vial before injection. This means that two-thirds of the drug substance is wasted. A close relationship during the development phase between the primary packaging manufacturer and the filling company can help to minimise overfill and lead to significant cost savings for the client.

Bubble-Free Process

When required for a specific project, Swissfillon can offer vacuum filling in order to remove or reduce residual air in the system. This is important for a number of reasons:

- Denaturation of a protein-based product could start at the fluid-air interface.

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- The container may be exposed to variations in pressure during transport, leading to stopper movement and loss of sterility of the product.
- Final sterilisation which involves vacuum can be carried out more easily if the bubble is smaller.
- Any air in the container must be expelled before an injection can be administered, and this will result in loss of the drug substance.
- If the drug has a high viscosity, any existing small air bubbles cannot be removed and so would be injected into the eye.

Stoppering

Implementation of the stoppering process on a filling line can be highly complex when using very small stoppers to close 0.5 mL prefilled syringes. In addition, the behaviour of stoppers developed for the ophthalmic market (i.e. silicone oil-free) means that the DP manufacturing requires an even higher level of expertise and know-how from the contract development and manufacturing organisation (CDMO) to guarantee that the stoppers are correctly transported and positioned and are not damaged.

SWISSFILLON ADVANTAGES MEET OPHTHALMIC DP REQUIREMENTS

Due to the many complexities and specific requirements for ophthalmic DPs, a drug manufacturer can minimise risks by working with experts who have a proven track record and who are able to offer the latest technology.

Swissfillon's key principles are readiness and communication. Time to market is often a key factor in the success of a new product and one of the most critical steps is the time taken to establish a process on its filling machine. This requires discussions on the best way to work together so that the solution can be achieved on the machine in the shortest possible time. Tiny details in the process can have a huge impact on the finish, and it is vital to optimise the overall value chain.

> "A drug manufacturer can minimise risks by working with experts who have a proven track record and who are able to offer the latest technology."

Swissfillon's filling line provides exceptional flexibility, accuracy and efficiency, with a 100% automated filling process in which every glove intervention is documented, 100% tare and gross weighing to deliver high accuracy on extremely low filling volumes, and 100% stopper setting control to minimise bubbles. Swissfillon is confident that it offers a best-in-class solution for ophthalmic drugs and can provide reliable and optimal solutions to meet your product's specific requirements.

ABOUT THE COMPANY

Swissfillon is a CDMO for complex injectables, providing aseptic DP manufacturing (filling) services to pharmaceutical and biotech companies which ensure the highest quality and security, and fully cGMP compliant services for high-value and difficult-to-fill products.

With its innovative, fully automated and highly flexible filling line at its facility in Visp, Switzerland, Swissfillon provides manufacturing capacity for vials, syringes and cartridges, resulting in a batch size of up to 15,000 units, when the product is too complex for small (manual) DP manufacturing or when the larger manufacturers are fully utilised for large quantities.

The advanced manufacturing technologies which the company has implemented for ophthalmic products also offer a competitive edge for other therapeutics. We will further discuss the importance of primary container selection and effective partnerships between pharma / CDMO / syringe manufacturers in coming issues.

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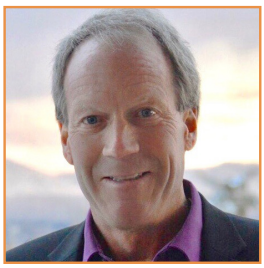

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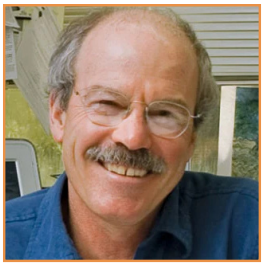

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THE PIVOTAL ROLE PLAYED BY DEVICE DEVELOPERS TO IMPROVE PATIENT EYE CARE

In this article, Zoë Davidson, Global Category Manager – Ophthalmic, and Carolyn Rose, Leader, Design Research, both at Nemera, discuss the challenges glaucoma and dry eye patients face with eye drop administration and present the Novelia® system featuring patented PureFlow® technology, which controls the medication flow.

INCREASING PREVALENCE OF CHRONIC EYE DISEASE

Dry eye disease is among the most common diseases in ophthalmology, with a prevalence of between 5% and 34%. Studies from specialist centres have found higher prevalence of up to 57%. Dry eye leads to more frequent patient-doctor contact than glaucoma.[1]

Glaucoma is a chronic, progressive optic neuropathy and a leading cause of blindness. In 2020, it was estimated that approximately 80 million people have glaucoma worldwide, and this number is expected to increase to over 111 million by 2040.[2] An increase in teleworking as a result of covid-19 has been a contributing factor to an increase in "digital eye strain". In addition, Google search activity analysis using Google Trends revealed that "sore eyes" were reported as the most significant ocular symptom of covid-19, with a significant spike in the number of Google searches over the last 10 months.

"Our eyes were not designed to use computers, especially for long periods of time – and, as a result, many people who spend long hours reading or working on a computer experience eye discomfort and vision problems," said Barbara L Horn, OD, President of the American Optometric Association.[3]

Novelia®, Nemera's preservative-free multidose eyedropper, has over 200 references on the market for prescription

Figure 1: (A) Cosopt iMulti® for the treatment of intraocular pressure in patients with open-angle glaucoma using Novelia®, marketed by Santen (Image courtesy Santen). (B) 76% of patients prefer Novelia® preservative-free multi-dose eyedropper.

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and over-the-counter (OTC) use, with 86% of these products dedicated to dry eye and glaucoma treatments (Figure 1A). A study was conducted by Nemera's R&D department, Insight Innovation Centre, in August 2020 to understand challenges encountered by dry eye and glaucoma patients with their current medication. A total of 16 participants were included in the study. This group included patients under treatment for dry eye and glaucoma, ophthalmologists and nurse practitioners forming the healthcare professional (HCP) sample. The participants were asked to briefly discuss their background and experience as it related to managing their/their patients' eye condition including symptoms, current therapies and treatment practices, as well as relevant challenges or frustrations.

GLAUCOMA VERSUS DRY EYE SYNDROME (REGIMENTED VERSUS REACTIVE)

While the patients involved in Nemera's study did not experience daily symptoms, glaucoma patients were still very aware that medication non-compliance can lead to vision loss, which motivates them to take their medication regularly. It has been found that the most important factor in the management of glaucoma patients is educating them about the disease of glaucoma itself.[4] Failure to acknowledge local symptoms and underplaying them as subjective disturbance can be highly detrimental.[1]

Glaucoma patients have set regimens as prescribed by their provider and have commonly fit this regimen into their morning/nightly routine. Thus, very few reported forgetting to take their medication or struggling to remember to do so. Note that Nemera's sample had "simple" regimens (e.g. 1–2 drops in the morning and/or at night), but physicians noted regimens can become more complex (multiple types of drops, 3–4 times/day). Additionally, some patients may use OTC dry eye drops, as irritation can be a side effect of some glaucoma medications. According to a 2008 survey conducted in Germany, over 50% of all glaucoma patients have dry eye. In addition, dry eye was more common if three or more anti-glaucoma agents were used as well as with increasing duration of glaucoma, suggesting preservatives have an influence on the development of dry eye.[5]

> "Controlling the number of drops that are delivered was the most cited complaint from both dry eye and glaucoma patients. Patients noted more than one drop may come out at a time or even leaked a bit before being squeezed. This becomes even more problematic when the bottle is almost empty, as patients must squeeze harder to get the drop(s) out and feel they have even less control."

The hypovolaemic dry eye is manifested clinically as symptoms of a feeling of dryness, a feeling of a grain of sand or foreign body in the eye, and stinging. The eyes often feel tired and symptoms typically only occur during the day during stress.[1]

Contrary to glaucoma sufferers, dry eye patients manage their condition as needed. They will experience dry eye symptoms (i.e. irritation, dryness, a "scratchy feeling") usually as a result of an activity (e.g. extended computer/screen time, wearing contact lenses, etc) or their environment (e.g. wind, seasonal allergies, etc).

Most patients will take drops (1–4 at a time) as needed throughout the day when they start to experience symptoms. Because of this, they typically carry drops with them (in a bag or pocket) throughout the day and/or store bottles in different locations where they might need them (e.g. at work or in the car).

More severe dry eye sufferers may take a drop first thing in the morning or at night as recommended by their provider, or use a prescription-grade medication.

PATIENT CHALLENGES DURING DROP ADMINISTRATION

During the study, patients commonly cited two key challenges relating to eye drop administration, the first of which being *lack of control*.

Controlling the number of drops that are delivered was the most cited complaint from both dry eye and glaucoma patients. Patients noted more than one drop may come out at a time or even leaked a bit before being squeezed. This becomes even more problematic when the bottle is almost empty, as patients must squeeze harder to get the drop(s) out and feel they have even less control.

While a minor annoyance to dry eye patients, this is more impactful for glaucoma patients who are unsure if they have received the correct dose and/or are concerned about running out of their expensive medication prematurely.

Another challenge cited by patients was the *uncertainty around remaining drops*. Many eye dropper bottles on the market today are opaque and those that are not are predominately covered by the label. This makes it difficult to see how much remains. And, even if you are able to see, it is difficult to know how many doses/drops that volume equates to. Many patients described shaking the bottle to "guesstimate" how many doses remain.

Dry eye patients can typically purchase another OTC bottle if they run out, but for glaucoma patients, whose refills are regulated by insurance (US-based study), there can be uncertainty and concern regarding the amount remaining (particularly if multiple drops had unwittingly been administered and/or refills are not automated).

LIMITING FACTORS FROM THE HCP PERSPECTIVE

Self-administration can be challenging for patients with arthritis, tremors and/or hand strength/dexterity issues that can make removing the cap, gripping and squeezing the bottle, and holding the hand steady during administration challenging.

Additionally, as described by physicians, there is a subset of patients who do not do well putting things into their eyes. These patients may require aiming techniques and ways to hold the eyelid steady (to avoid blinking). In a worst-case scenario, these limitations may preclude self-administration, requiring a caregiver.

Compliance was also noted as a challenge by all HCPs, who commonly noted this becomes more of an issue with more complex regimens. Nearly nine out of 10 glaucoma patients are unable to instil eye drops correctly and therefore an easy-to-use system that is appreciated by patients

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> "Novelia's patented PureFlow® technology not only serves as a venting system but also controls the medication flow. Nemera has adapted the flow control within Novelia® that avoids multiple drop delivery into the eye and ensures that only one calibrated drop is dispensed at a time."

could contribute to improving their compliance with a treatment.[6] One HCP who participated in the study stated that: "When you have one drop, compliance is 75–80%. When you use two drops, it drops to 65%. If three drops, it drops below 50%".[7]

Additionally, patients (especially those with cognitive issues) may not always remember or follow storage and administration instructions such as refrigerating the medication or shaking before use.

PATIENT EYE CARE MANAGEMENT AND HOW NOVELIA® OFFERS A SOLUTION

Control

Patients and HCPs alike desire a bottle that allows users to control the number of drops delivered, consistently delivering a single drop with each actuation.

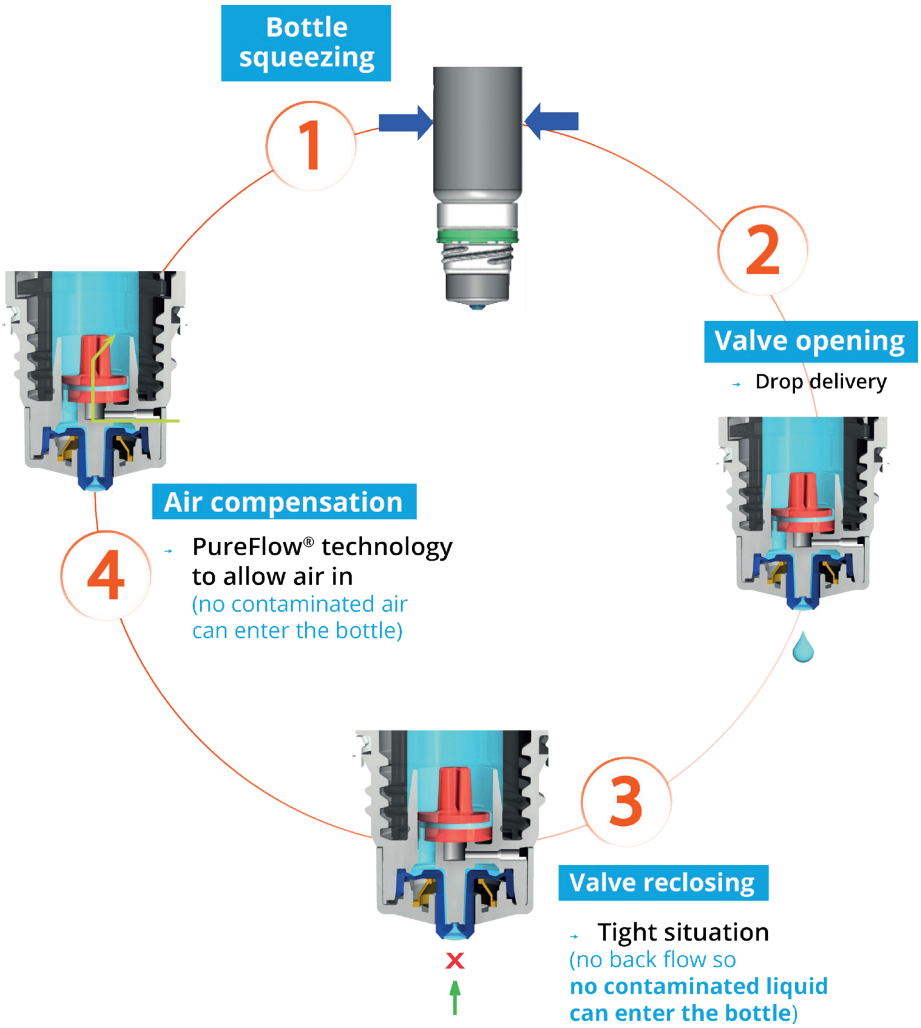

Figure 2: The Novelia® system uses a non-return valve that removes the need to filter the liquid, making it possible to use a silicone membrane to filter the air.

Novelia's patented PureFlow® technology not only serves as a venting system but also controls the medication flow (Figure 2). Nemera has adapted the flow control within Novelia® that avoids multiple drop delivery into the eye and ensures that only one calibrated drop is dispensed at a time. Nemera offers three different PureFlow® versions, each tailored to formulations of differing viscosities, from highly liquid to highly viscous. In addition, five different valve sizes are available, each one delivering a different calibrated drop size. This allows Nemera to customise the drop size depending on specific product requirements. This improved control leads to increased patient confidence (of accurate dosing), and reduced frustration and medication waste.

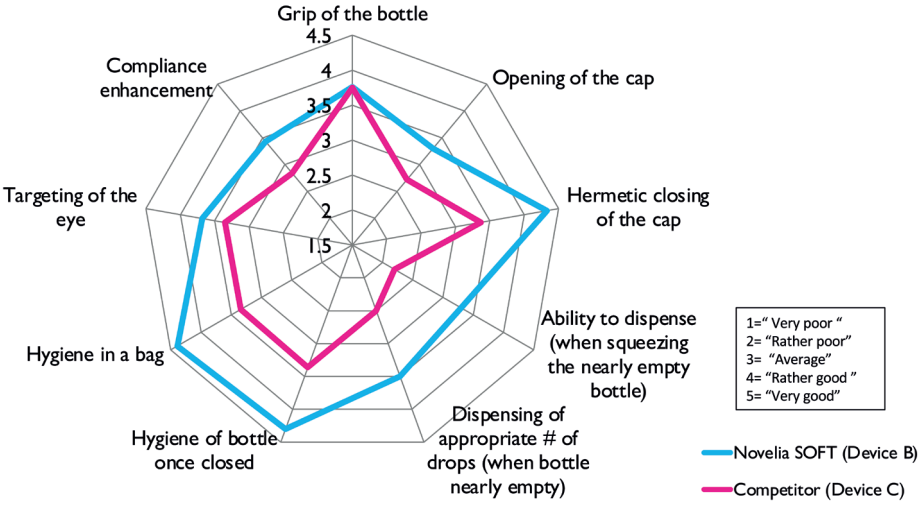

Figure 3: Mean scores across different parameters given by 90 patients with glaucoma, dry eye or conjunctivitis using Novelia® and another marketed device.

Ease of Use

Users, even those with dexterity issues and tremors/shaking, must be able to effectively handle and manipulate the delivery system and administer a drop.

Contributing factors to Novelia® being the preservative-free multidose eyedropper preferred by 76% of patients included the intuitiveness of the screw-on cap and the associated reassurance and squeeze force required towards the end of the product's life. Novelia® required only 6% more pressure to

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squeeze the bottle from the beginning to the end of the treatment, compared with 35% for the other device (Figure 3).[8]

Novelia's® patented blue tip is also a favourite feature of the device. It helps patients target the eye before drop administration and anticipate the angle of the drop on to the ocular surface.

Transparency

Patients need more visibility of their medication supply, so they can replenish as needed and do not find themselves without.

A full range of bottles is available in terms of size, material and sterilisation type (5 mL, 7.5 mL, 11 mL and 15 mL). All sizes are available in low-density polyethylene either in white or natural (transparent), allowing patients to know when their medication is running low. Nemera is also developing polypropylene and cyclic olefin copolymer bottles for specific formulation compatibility. Novelia® has been validated using both gamma and ethylene oxide sterilisation.

Portability

A user must be able to transport their medication easily. Note that for dry eye patients this is likely to be daily, while for glaucoma patients this is likely only for overnight/travel.

The Novelia® device features a screw-on cap that fits tightly on to the device nozzle, which is optimal in terms of portability. Patients have found other marketed devices comprising a snap-on cap to be less robust, with several instances of leaking during transport, be it in a handbag or pocket. As such, Novelia® outperformed another marketed device in terms of cap opening, hermetic sealing and nomadic use, with a mean score of 4.5 out of five for the three features.[9]

WHAT IS NEMERA PUTTING IN PLACE TO CONTINUE TO SERVE CUSTOMERS IN THE OPHTHALMIC SPACE?

To serve customers in supporting patient needs, Nemera has recently extended its manufacturing capabilities and, in doing so, has doubled its capacity to produce the Novelia® preservative-free multidose eyedropper (Figure 4).

Figure 4: Nemera's headquarters in La Verpillière, France, has doubled its capacity to produce the Novelia® preservative-free multidose eyedropper.

In addition to Nemera's continued investment to support the production side, Nemera is equally reinforcing its offering in services. Nemera firmly believes that developing a holistic and comprehensive patient experience and human factors management strategy can create significant competitive advantages and, ultimately, result in safe, effective and differentiated combination products that respond to patient needs.

Nemera continues to offer a range of laboratory services, including testing of customers' bulk formulation, allowing Nemera to determine the best Novelia® configuration for a formulation. Nemera can recommend the most suitable PureFlow® control, bottle type and valve size to achieve the desired drop calibration.

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

In conclusion, Nemera's unwavering commitment to address patient needs and translate them into meaningful solutions truly differentiates the combination products offered across its delivery routes, including ophthalmology.

ABOUT THE COMPANY

As a world-leading device combination solutions provider, Nemera's purpose of putting patients first enables it to design and manufacture devices that maximise treatment efficacy. Nemera is a holistic partner and helps its customers succeed in the sprint to market. From early device strategy to state-of-the-art manufacturing, Nemera is committed to the highest quality standards. Agile and open-minded, Nemera works with its customers as colleagues. Together, they go the extra mile to fulfil their mission.

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ABOUT THE AUTHORS

Zoë Davidson is the Global Category Manager for Nemera's ophthalmic franchise, including the preservative-free multidose eyedropper, Novelia®. Mrs Davidson joined Nemera in January 2017 as part of the business development team, responsible for ophthalmic products, before transitioning into the category manager role during the summer of 2019. Graduating in 2013 from Strathclyde Business School in Glasgow, Scotland (ranked amongst the top 10 business schools in the UK), Mrs Davidson studied International Business and Modern Languages. Prior to her move to Lyon, France, and joining Nemera, Mrs Davidson held the position of International Marketing Executive for an award-winning independent company in the UK tourism industry.

Carolyn Rose is the Leader of Design Research at Nemera's Insight Innovation Centre, where research is leveraged to better understand the patient journey and user needs to help inform product development for both Nemera and global clients. Ms Rose has worked for nearly 20 years in design research, generating meaningful insights and defining actionable market opportunities. Her human-centred and process-oriented approach aims to better understand the behaviours, expectations and motivations of end users, as well as the environments, attitudes and trends that shape them. She has a Bachelor of Industrial Design from Syracuse University (NY, US) and a Master of Design Methods and Strategy from The Institute of Design (Chicago, IL, US).

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DRUG DELIVERY TO THE EYE: OVERCOMING THE CHALLENGES OF INTRAVITREAL PREFILLED SYRINGES

In this article, Suresh Gupta, PhD, Head of Human Factors and Usability Engineering, UK, of Cambridge Consultants discusses the challenges of developing a PFS product for intravitreal injection, highlighting how designing for the intravitreal space, rather than the standard parenteral, imposes a number of additional requirements on the design.

In the field of ophthalmic drug delivery, intravitreal injections using prefilled syringes (PFSs) are becoming increasingly prevalent – improving patient treatment and outcomes by delivering an efficacious shot of medicine directly into the eye. Opportunities abound in this still-evolving area of ocular therapy innovation, but significant challenges remain. For example, a surface-level examination might make adapting the design of a standard parenteral PFS for intravitreal use seem relatively straightforward. However, that's a long way from the reality.

This article explores the theme of delivery to the eye, a growing area of interest in ophthalmology that spans drugs, implants and gene therapies. It will unpack the challenges of PFS development, drawing on the author's professional experience to reveal how innovators can best begin to plot a path to success.

> "A surface-level examination might make adapting the design of a standard parenteral PFS for intravitreal use seem relatively straightforward. However, that's a long way from the reality."

To begin with, let's consider PFSs, first used by healthcare professionals and patients for parenteral (administered anywhere other than the mouth and alimentary canal) injections under the skin or into the muscle. It is only in recent years that PFSs have made their way into the field of intravitreal injections. These injections deliver drugs directly into patients'

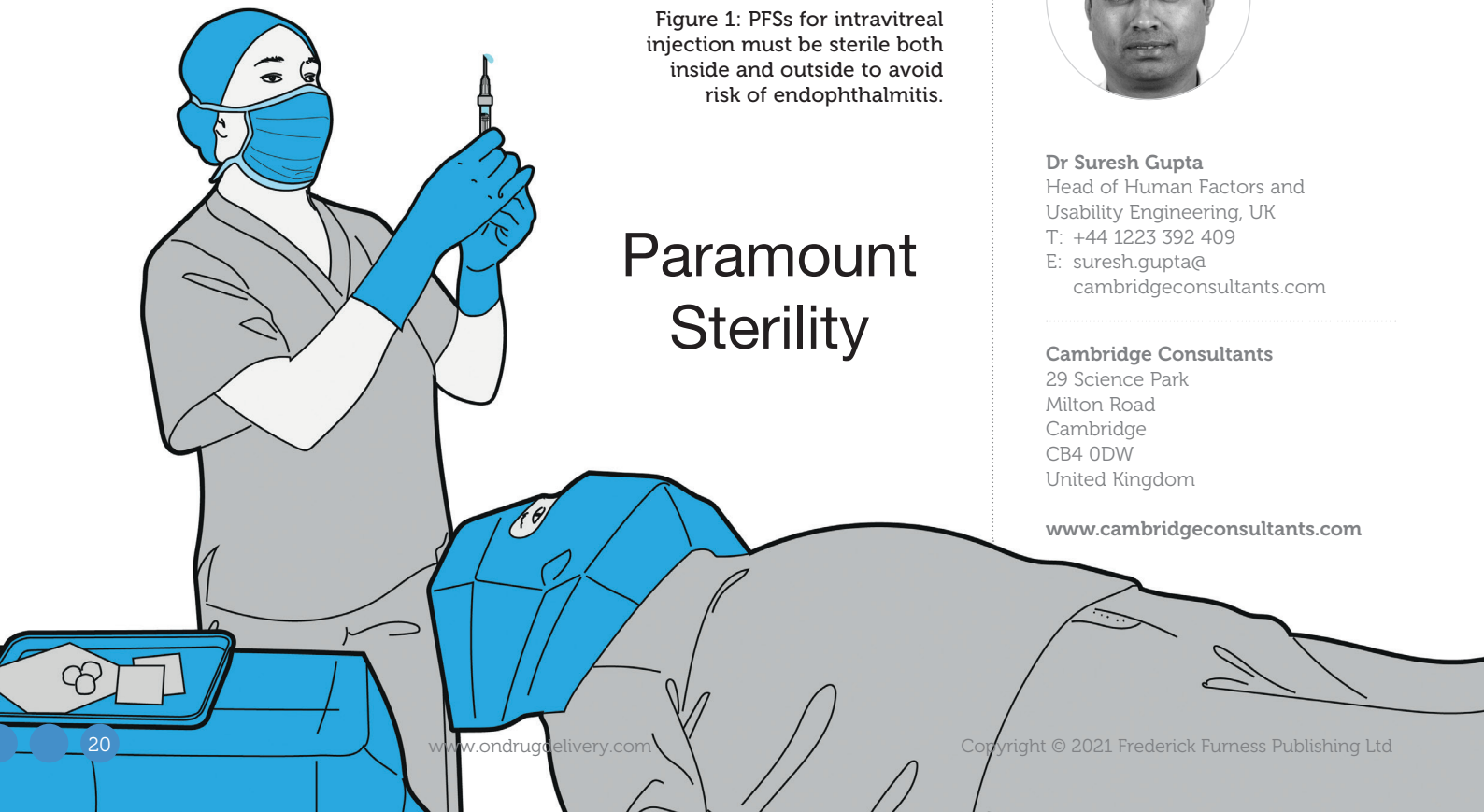

Figure 1: PFSs for intravitreal injection must be sterile both inside and outside to avoid risk of endophthalmitis.

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eyes for the treatment of conditions such as wet age-related macular degeneration (AMD), diabetic retinopathy and diabetic macular oedema. Examples include Genentech's Lucentis® (ranibizumab) and Regeneron's Eylea® (aflibercept), both anti vascular endothelial growth factor (VEGF) injections that come in a ready-to-use PFS.

At first glance, it might look as if the same PFS design has found its way into the intravitreal injection space. But the devil is in the details. Together with colleagues, the author has made the PFS journey from standard parenteral to intravitreal application. So, let's highlight some of the key differences and challenges when it comes to PFSs for intravitreal injections, compared with designing for the standard parenteral space, and discuss some potential improved solutions based on publicly available information.

TACKLING THE ISSUE OF STERILITY

Endophthalmitis, an inflammation of the interior cavity of the eye most commonly caused by an infection, is a major concern associated with intravitreal injections. It poses a significant challenge with respect to maintaining the sterility of the clinical environment in which the injection takes place, and also in terms of how the sterility of the PFS and its contents is achieved and maintained throughout manufacturing, shipment, storage and use.

A key difference between an intravitreal and standard parenteral PFS is that the former must be sterile both inside and outside, whereas the latter does not have to be sterile on the outside (Figure 1). What might sound like a simple additional requirement poses a tremendous challenge to the design, manufacture and packaging of an intravitreal PFS. This challenge spans the syringe material that protects the contents from the ambient air; the design that enables aseptic filling of the drug content and preserves it during shipment, storage and use; the packaging that allows terminal sterilisation and ease of unpacking without compromising sterility; and the design that facilitates ease of use and reduces use errors.

ENSURING DOSE ACCURACY

Intravitreal injections are typically very small doses of 50 µL or less, equivalent to a drop of liquid. When you compare this dose with a 1 mL standard parenteral PFS, the delivered volume is 20 times smaller. Any slight deviation from the intended dose could result in a significant underdose or overdose in terms of both percentage and therapeutic effect (Figure 2). For example, if there is an error of 20 µL for a 1 mL standard parenteral PFS, it would cause a 2% inaccuracy in the dose, whereas the same error in an intravitreal injection would cause a 40% underdose or overdose – a big difference!

An underdose of such magnitude for an intravitreal injection may mean a compromised therapeutic effect – or no therapeutic effect at all – whereas an overdose into an eye, which is roughly 20 mm in diameter, could cause detrimental intraocular pressure (IOP) and, in rare cases, drug toxicity and other complications.

So, what are the design challenges when it comes to achieving a dose accuracy with an intravitreal PFS? The answer can be found by first understanding the sources of dose inaccuracies. There are a number of possibilities:

- Tolerances in the bore diameter of the syringes
- Inconsistencies in the shape of the neck of the syringes
- Irregularities in the geometry of the stoppers
- Unpredictability of the dead volumes of the syringes and needles.

"A key difference between an intravitreal and standard parenteral PFS is that the former must be sterile both inside and outside, whereas the latter does not have to be sterile on the outside. What might sound like a simple additional requirement poses a tremendous challenge to the design, manufacture and packaging of an intravitreal PFS."

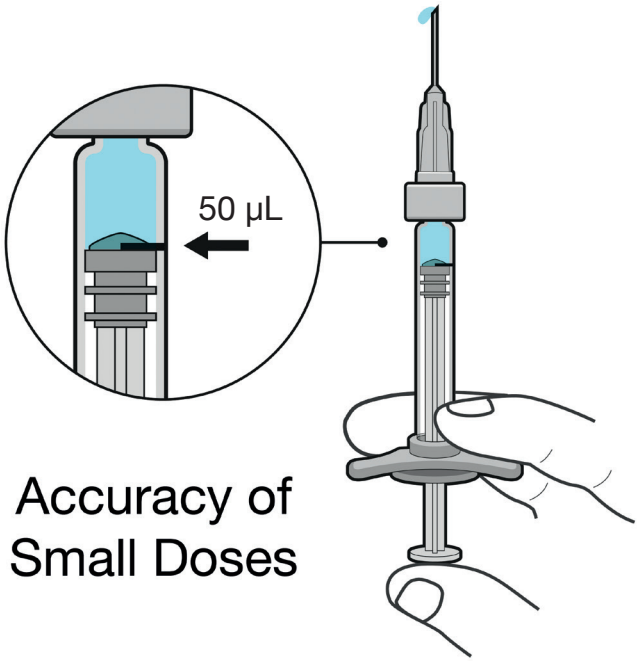

Figure 2: Intravitreal injections deal with doses of 50 µL or less, so even very small errors in dose can have significant impact.

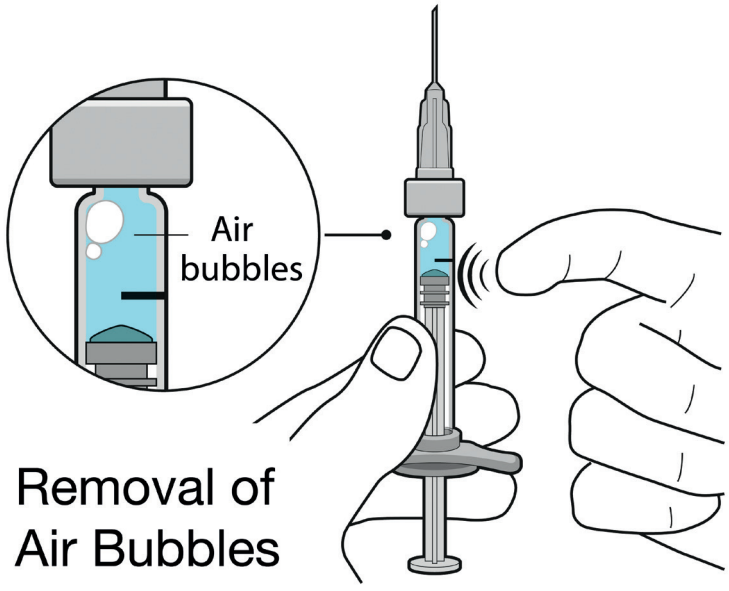

Figure 3: Air bubbles in PFSs for intravitreal injection can cause complications, and can take up space inside the syringe that significantly lowers the delivered dose.

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"Even when all the design- and manufacturing-related sources of inaccuracies have been addressed or compensated for, it is still difficult to predict and control users' behaviour."

The other most likely source is the usability of the product. One such issue could be a user's inability to remove any air bubbles and align the stopper precisely with the dose mark (Figure 3). Therefore, the solution lies in the manufacturer's ability to minimise or eliminate the sources of inaccuracies, compensate for any residual potential inaccuracies (e.g. over-filling of the PFS) and incorporate thorough human factors engineering into the development process.

Even when all the design- and manufacturing-related sources of inaccuracies have been addressed or compensated for, it is still difficult to predict and control users' behaviour. Will they decide to align the tip of the stopper with the dose mark? Or will they align the mark with one of the ribs on the stopper? Or maybe they use the flat bottom of the stopper as it looks like a more defined reference point. These are some of the genuine behaviours exhibited by experienced ophthalmologists and retina specialists.

Needless to say, if one aligns the bottom of the stopper with the dose mark with some of the marketed intravitreal PFSs, they are unlikely to deliver any drug at all, without even realising it. Imagine this from the patient's perspective; they have undergone all the pain and inconvenience, not to mention the risks, of an intravitreal injection for nothing. To top it off, they may be self-funding their expensive treatment (or, in this case, non-treatment) and their condition may deteriorate further as a result.

DEALING WITH BUBBLES AND FLOATERS

A PFS injection containing small air bubbles delivered into subcutaneous tissues may not have much effect on the patient. But an injection of air bubbles into a patient's vitreous cavity may cause complications. This is another important difference between a standard parenteral and intravitreal PFS products. Although literature suggests that an injection of small air bubbles into an eye is likely to get resorbed within a couple of days, it may affect vision temporarily due to bubble-related floaters. Large air bubbles, on the other hand, could result in a high IOP and related complications.

Another concern with air bubbles is that they tend to stick to the syringe wall and get trapped within the dead spaces, making them hard to expel during priming of the syringe. These bubbles then take up a significant proportion of the 50 µL volume, and therefore compromise the actual amount of medication delivered to the eye. In the worst case, air bubbles, if drawn from the ambient air during priming (design allowing), may result in an infection of the eye – one reason why the Lucentis® PFS plunger rod is not attached to the stopper.

Besides air bubbles, other particulates, such as droplets from the lubricant (usually silicone) used to facilitate smooth stopper movement and fine particles that have rubbed off from the stopper or syringe wall, may also cause floaters and other complications in a patient's eye. On the other hand, most of these may have no effect or cause only a minor local irritation to the skin with a standard parenteral injection.

So, what are the design challenges and the solutions? The following are all key to the success of an intravitreal PFS:

- The selection of the syringe, plunger, cap material and a state-of-the-art manufacturing process (for example, the low siliconisation achieved by Lucentis®) to reduce particulates
- Using bubble-free filling technologies
- Ergonomic design of the user-interface
- Effective instructional materials tested and validated via human factors studies.

"There are many opportunities for significant use errors – not removing the air bubbles, not setting the dose accurately and failing to maintain sterility during use. All of these errors could result in harm to patients and compromise their treatment considerably."

IMPROVING USABILITY AND EFFICIENCY

The likelihood of potential use errors and their consequences are greater with an intravitreal injection compared with a standard parenteral injection. For example, if a user inserts the needle of a subcutaneous PFS into the skin at a 60° angle as opposed to the intended 45°, it might hurt the patient a bit more or – in the worst case – compromise the injection's therapeutic effect to a very small degree.

But now let's think about the needle insertion into the eye for an intravitreal injection. It has to be precisely 3–4 mm away from the limbus towards the centre of the globe, or the needle may damage the lens or other internal tissues. As another example, if the user's hand moves whilst depressing the plunger with a standard parenteral PFS, the patient might feel a bit more pain or discomfort, or it may cause a minor laceration. But if this happens with an intravitreal injection, the consequence could be extremely severe (Figure 4).

There are many opportunities for significant use errors – not removing the air bubbles, not setting the dose accurately and failing to maintain sterility during use. All of these errors could result in harm to patients and compromise their treatment considerably.

Another important point of note from an ophthalmologist's or retina specialist's perspective is the efficiency of the use process. These experts perform a large number of intravitreal injections per day. Therefore, even a small reduction in time per injection would save them a significant amount of time overall, hence increasing their throughput.

Although it might appear that an intravitreal PFS has simple ergonomics and room for improvement in this area is limited, the application of a thorough human factors engineering process, coupled with a robust risk management system, will identify any potential use errors, appropriate mitigations and opportunities for improvement. The process focuses on understanding the users' needs (both obvious and latent), considering how subtle alterations to the user-interface could cater to those needs, and designing out problems through an iterative

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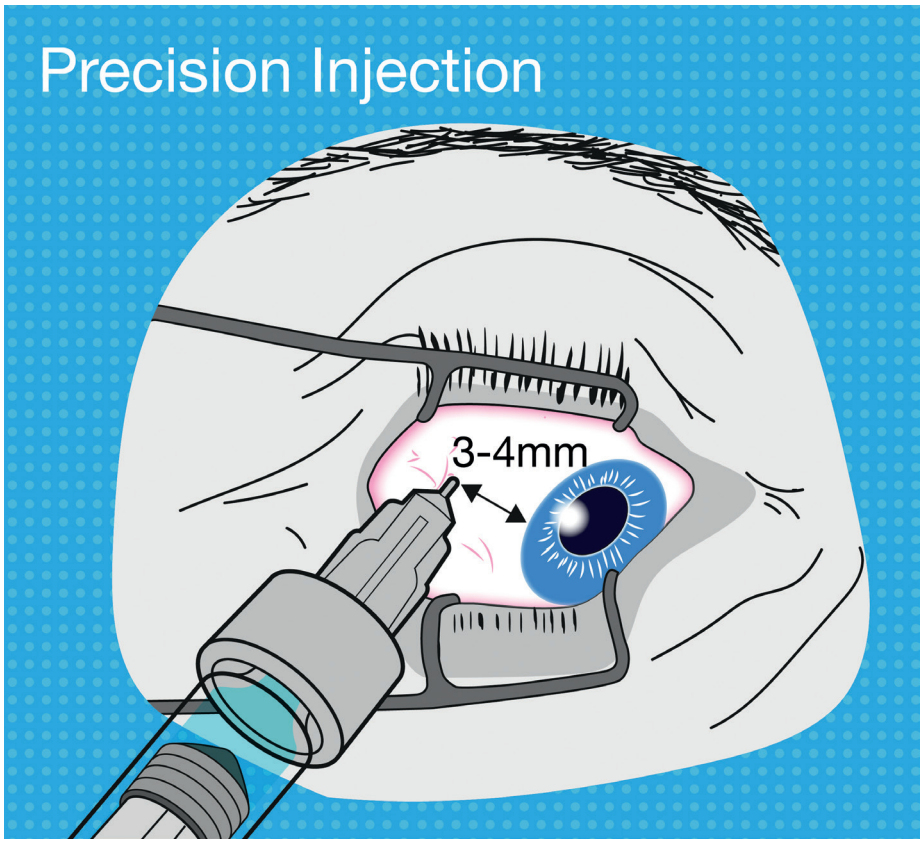

Figure 4: The tolerance for use error when performing an intravitreal injection is very low, so intravitreal PFS design should aim to be as ergonomic as possible.

process of evaluation and improvement. All this makes the product safe and effective, with the addition of increased user satisfaction.

LOOKING BEYOND INTRAVITREAL PFSs

It is fair to say that intravitreal PFSs currently on the market have tackled some of the many challenges very well.

> "Perhaps it's also time to look beyond intravitreal drug delivery to suprachoroidal and subretinal injections, which focus on providing localised delivery of existing treatment options and of new gene and cell therapies, improving outcomes and minimising side effects."

But it's important to remember this: with a rich domain knowledge and critical design thinking, intravitreal PFS design can be improved further, as some challenges still persist. Moreover, even if a new manufacturer wants to achieve only what these marketed products have achieved, they must consider the intellectual property (IP) around some of the design solutions. It is a narrow design space fraught with challenges.

Maybe the next step is to look beyond the use of a PFS, and also outside the intravitreal space. The science is evolving and so too have some of ophthalmic treatment methods and approaches. For example, some of sources suggest that biodegradable and non-biodegradable implants are an effective way of providing sustained drug delivery to eyes, thereby improving the treatment outcomes.

Perhaps it's also time to look beyond intravitreal drug delivery to suprachoroidal (the space between the sclera and choroid that traverses the circumference of the posterior segment of the eye) and subretinal (beneath the retina) injections, which focus on providing localised delivery of existing treatment options and of new gene and cell therapies, improving outcomes and minimising side effects. These new methods require sophisticated, but not necessarily complex, delivery systems. As the technology advances, we will certainly see more treatment options for patients as well as great opportunities for device manufacturers.

ABOUT THE COMPANY

Cambridge Consultants, part of Capgemini Invent, develops breakthrough products, creates and licenses IP and provides business consultancy for technology-critical issues for clients worldwide. For over 60 years, the company has helped its clients turn business opportunities into commercial successes, whether they are launching first-to-market products, entering new markets or expanding existing markets by introducing new technologies. With more than 900 staff, including engineers, scientists, mathematicians and designers, based in offices in Cambridge (UK), Boston (US), Tokyo (Japan) and Singapore, Cambridge Consultants offers solutions across a diverse range of industries, including medical and life science, industrial, consumer, communications and infrastructure.

Dr Gupta and his colleagues have a wealth of experience in the subtle design challenges and IP complexities in the intravitreal drug delivery space, and a keen understanding of the various needs involved, and would be happy to discuss the topic in more detail.

ABOUT THE AUTHOR

Suresh Gupta is Head of Human Factors and Usability Engineering at Cambridge Consultants, UK. He has extensive experience in managing, leading and providing human factors expertise in the field of medical device and combination product design and development, including products such as drug delivery devices, diagnostic devices, surgical and acute care devices. Dr Gupta has a particular interest in ophthalmic drug delivery devices and has helped many clients achieve their goals in this space. He has a wealth of experience in supporting regulatory submissions worldwide. Dr Gupta has a PhD in Engineering Design, specialising in human factors, from the University of Cambridge (UK).

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