OPHTHALMIC DRUG DELIVERY

ON drugDELIVERY

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AERO PUMP
AKRIVISION TECH TARGET EYE FOR SIGHT
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ONdrugDelivery Issue N° 157, March 18th, 2024

OPHTHALMIC DRUG DELIVERY

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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ACCURATE DELIVERY AND PRECISE DOSING OF EYE DROPS: WHAT IF WE CHANGE THE INSTILLATION PROCEDURE?

In this article, Philippe Daull, PhD, Co-Founder and Chief Executive Officer, and Pierre Roy, Co-Founder and Chief Technology Officer, both at Akrivision Technologies, discuss how changing the administration procedure for eye drops can improve the patient experience and eliminate health risks.

Topical ocular administration of drugs is a critical component of the treatment of ocular diseases, such as glaucoma, dry eye disease, Sjögren's syndrome and allergies, to name a few. Currently, the most common way to administer treatment to the eye is through the administration of an eye drop via the use of a multidose (MD) eyedropper. The eye drop delivers the medication directly to the affected area, providing local and immediate relief.

For the past 70+ years, administering an eye drop required the patient to tilt their head backwards, raise their arm above their head and, in this uncomfortable position, perform the delicate operation of targeting the eye and controlling the squeezing force to expel a single drop from the MD eyedropper, and all without a clear visual of what they are doing. Administering an eye drop is neither straightforward or easy.

Received wisdom confirms that the accurate delivery of a single, well-calibrated drop remains a challenge for a very large proportion of patients, especially for elderly or visually impaired patients. The most frequent problems encountered are difficulty targeting the eye (up to 76% miss the eye completely), uncontrolled number of drops expelled upon squeezing (up to 64% of the patients dispense more than one drop) and frequent inadvertent contact between the tip of the MD eyedropper and the eye structures (studies show that

> "Received wisdom confirms that the accurate delivery of a single, well-calibrated drop remains a challenge for a very large proportion of patients, especially for elderly or visually impaired patients."

Issues with eye drop administration	Frequency	Risks
Overall failure rate[19–23]	13%–91%	Non-adherence, disease progression and vision loss
Contamination of eyedropper tip through contact with the eye or lid[19–22,24–27]	18%–76%	Eye infection Cornea trauma following inadvertent contact with the tip
Missing the eye[20,21,24,25]	10%–76%	Disease progression Multiple attempts, product spillage
Difficulty aiming[28]	49%	Periocular side effects Multiple attempts, product spillage
Dispensing more than one drop[20,21,27,29,30]	11%–64%	Side effects (ocular and periocular) Product spillage, increase cost for treatment, over-prescription
Difficulty squeezing[28]	20%	Stop treatment, disease progression

Table 1: Common issues with the instillation of eye drop medications with existing MD eyedroppers and their associated risks.

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the tips have been contaminated in almost 80% of patients' MD eyedroppers).[1,2] Table 1, adapted from Hovanesian *et al*, summarises the main issues associated with the instillation of eye drops and their related risks.[1]

The difficulty with administering eye drop medication is the root cause of significant health risks for patients, including poor compliance and treatment cessation, leading to disease progression, poor quality of life and vision loss.[3–6] Note that forgetfulness, complicated dosing regimens, ocular or periocular side effects (due to overdosing) and the cost of eye drop medication are also associated with the poor compliance observed in patients with chronic eye diseases, such as glaucoma and Sjögren's syndrome.

Eye infection, resulting from tip contamination of MD eyedroppers, has often been identified as a potential risk for ocular health. However, even though the majority of MD eyedropper tips are contaminated following inadvertent contact between the tip and the eye structures (cornea and conjunctiva) or the eyelids and eyelashes (up to 80%, see Table 1), or simply from the environment, the US FDA's Ophthalmic Devices Panel of the Medical Device Advisory Committee (MDAC) states: "It may be concluded that the ophthalmic dispensers are generally low in risk".[7]

The healthy microbiome naturally present on the ocular surface, which is closely related to the microbiome of the eyelids, has been demonstrated to protect the eye from pathogenic infection.[8–11] Indeed, the low prevalence of eye infection observed over the past decades – despite the long history of use of MD eyedroppers with tips contaminated with patients' own ocular/eyelid microbiome – explains why the MDAC views MD eyedroppers as "low in risk". This must be distinguished from the recent warning letters issued by the FDA for a potential risk of eye infection following the use of eye drops and recalls that were related to unsanitary conditions and sterility breaches of critical drug production areas at the manufacturing facility, with the subsequent possible contamination of the incriminated MD eyedroppers' content during the manufacture of the drug product.[12–14]

It is very important that eye drop formulations are manufactured under sterile conditions and are adequately protected, either with effective preservative agents or preservative-free MD eyedroppers for the safe use of the eye drop medication.[15]

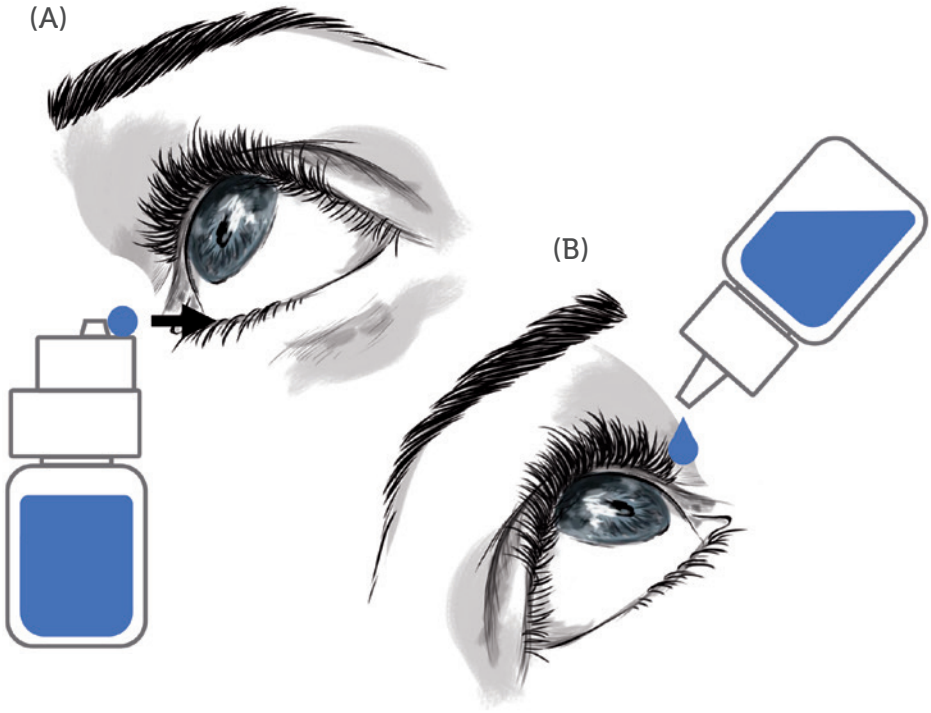

Figure 1: The application vs instillation of eye drop medication. A) Application: the patient keeps their head straight, and upon opening of the conjunctival fold, the eye drop is transferred to the eye with the new MD eye bottle in an upright position. B) Instillation: the patient reclines their head backwards and let a drop fall into the eye, while the MD eyedropper is in an inverted position, raised above the head and pressed.

The difficulties of administering eye drops with existing MD eyedroppers led Menino *et al* to state that "new strategies must be developed, such as creating new containers that are easier to handle for the elderly".[16] This also suggests that existing MD eyedroppers are ineffective drug delivery devices, as they fail to accurately deliver a single, well-calibrated eye drop (Table 1), posing serious risks to patients' eye health and vision.

The administration procedure itself is at the heart of the issues and risks associated with MD eyedroppers. Since the procedure is directly linked with the design of existing MD eyedroppers, is it feasible for this design to progress towards a new drug delivery device where the complicated administration procedure is replaced by an easier and safer application procedure (Figure 1) that does not require patients to recline their head backwards, for example? Could those design changes benefit patients' health and quality of life?

> "The administration procedure itself is at the heart of the issues and risks associated with MD eyedroppers."

A redesigned MD eyedropper should:

- Resolve the administration difficulties faced by patients when they try to administer an eye drop, such as by changing the administration procedure itself.
- Be easy to use, giving patients better control of the administration procedure and more confidence in the fact that the eye drop is accurately delivered to the eye with no product spillage, such as by giving patients the ability to see what they are doing while administering an eye drop (i.e. removing the need for patients to recline their head backwards).
- Have reasonable manufacturing costs to better manage the expense of eye drop medication.

A new MD eye bottle that can be used in an upright position – allowing the patient to keep their head straight in a comfortable manner, does not need them to raise their arm and allows them to see and control what they are doing (through the use of a mirror or a smartphone in selfie mode) – should improve the patient experience and satisfaction with eye drop medication.

Figure 1 schematically illustrates this new concept, where the instillation procedure (where the eye drop falls on the eye) is replaced by an application procedure (where the eye drop is directly transferred from the drug delivery device to the conjunctival fold).

Table 2 highlights the key attributes that an MD eye bottle should possess to be a user-friendly, accurate and reliable drug delivery device.

Accurately applying a single, well-calibrated eye drop into the conjunctival fold of the eye is possible with the new MD eye bottle. Figure 2 illustrates the two actuation and application steps for accurate administration of an eye drop. Note that the patient can, at all times, easily see and control what they are doing. For actuation, a simple up and down movement enables the patient to easily expel a single, well-calibrated drop and put it on the hydrophobic delivery surface by pressing on the MD eye bottle when it is returned to its upright vertical position. The volume of the drop is independent of the pinching pressure and is governed by the internal design of the bottle.

The application requires the conjunctival fold to be gently opened with transient contact between the lower eyelid margin and the external rim of the new MD eye bottle. There is no need to touch the eyeball to transfer the drop (by capillary attraction) from the delivery surface to the tear film in the conjunctival cul-de-sac. In terms of eye infection risk, this application gesture is very close to the "closed eyelid instillation" recommended by the American Academy of Ophthalmology for children or people too anxious to administer an eye drop – the eye drop is deposited on the closed eyelid in the nasal corner of the eye and then rolls into the eye upon eyelid opening and blinking.[17] With this procedure, the eye drop may be contaminated by bacteria on the eyelid as it rolls into the eye.

Desired quality	Specific attributes
Easy to use	• Use new MD eye bottle in an upright position • No tilted head or raised arm position • See and control all steps of the drop application process throughout the process • Secure and stable application gesture (use the cheekbone as a guide) • Easy to understand the application process and how to use/orientate the new MD eye bottle ("look and feel") • Easy two-step application gesture – perform one action at a time (expel and apply the drop in a sequential manner)
Resolve the administration issues	• Accurately target the eye every time • Apply only a single eye drop • Well-calibrated eye drop (all drops of exactly the same volume – eye drop volume independent of the pinching pressure and bottle angle) • No product spillage • Eliminate the backwash of liquid (i.e. expelled liquid re-aspiration within the bottle) • Tip should not touch the eye (avoid cornea trauma, decrease contamination risk) • Head/nozzle delivery surface should be hydrophobic (to eliminate any residual liquid) • Easy to control the pinching pressure to expel a single eye drop (operation performed in a comfortable position – clear visual of the operation)
Affordable	• Simple design of the new MD eye bottle head/nozzle • Low manufacturing cost by injection moulding

Table 2: Desired qualities for a new user-friendly MD eye bottle.

To assess patient perception and acceptance of this change in application, a preliminary usability study with the new MD eye bottle was performed.[18] Sixteen patients (both naive and experienced with existing MD eyedroppers) were presented with the new MD eye bottle and the instruction leaflet. Following a two-minute demonstration of the correct use of the new MD eye bottle, patients were asked to test it. A questionnaire and a five-point Likert scale survey evaluated their understanding of the use instructions and their appreciation of the new application procedure. Patient feedback on the strengths, weaknesses and advantages over the existing MD eyedroppers was also recorded.

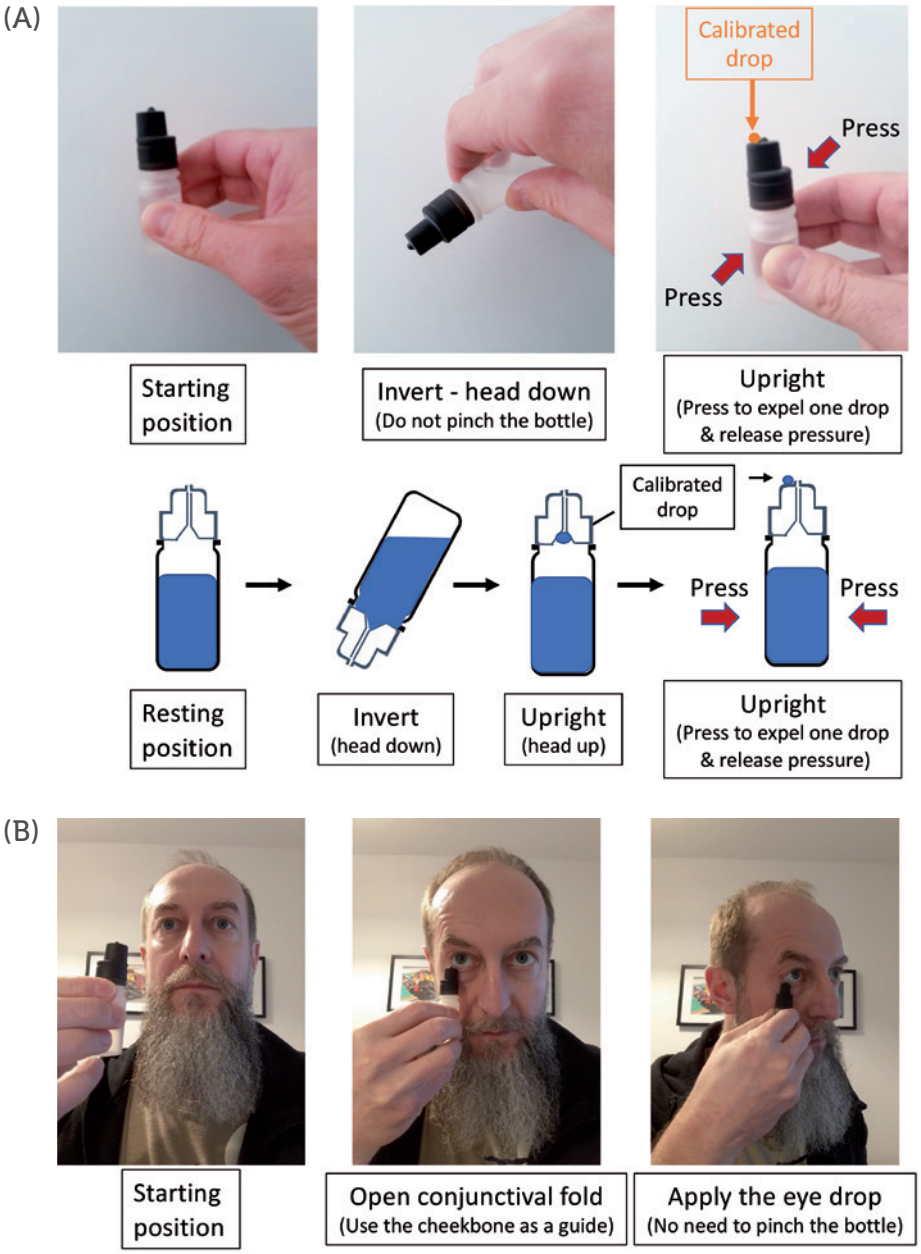

Figure 2: Schematic representation of the two-step application procedure of the new MD eye bottle. (A) actuation and (B) application steps of a single, well-calibrated eye drop with the new MD eye bottle.

> "Patients were particularly satisfied that the risk of product spillage is also reduced with the new MD eye bottle, and that the risk of touching the cornea is greatly reduced."

A total of 15 out of 16 (93.8%) patients preferred the new MD eye bottle over existing MD eyedroppers. The new application gesture was rated as easy to perform, and the new MD eye bottle was either very easy (75.0%) or easy (18.8%) to use for 15 out of 16 patients (Figure 3). Patients were particularly satisfied that the risk of product spillage is also reduced with the new MD eye bottle, and that the risk of touching the cornea is greatly reduced. The feedback was very positive, with comments such as: "Frankly easier"; "Much more convenient than classic droppers"; "You can even use it with glasses on, this is positive, you can see what you do"; "Gesture more evident compared to when you need to raise the arm. More comfortable for the neck"; and "It is convenient, and new. No spillage, you do not put liquid everywhere".

This usability study determined that this patient-centric design for the new MD eye bottle is easy to use and the new application procedure is well accepted. This new design improves patients' accuracy and ability to correctly deliver the right dose of treatment while reducing product spillage. By improving the topical ocular administration experience and satisfaction,

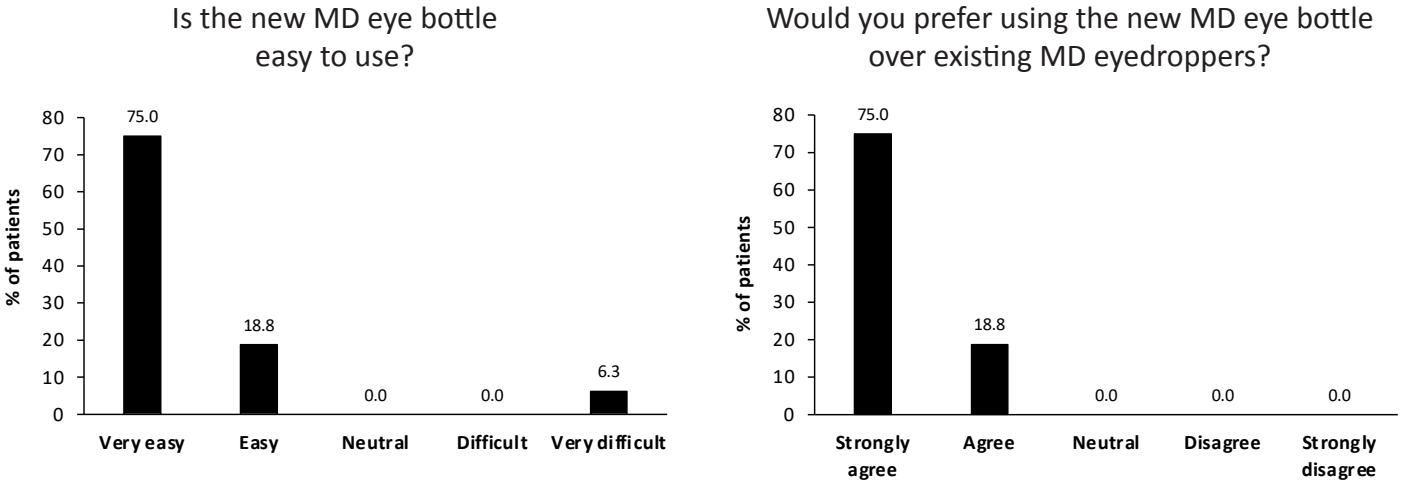

Figure 3. Usability testing results for new MD eye bottle.

the new design may help improve treatment adherence. The new MD eye bottle has the potential to better protect patients' vision and improve their quality of life.

In conclusion, it is possible to change the way eye drops are dispensed through a simple evolution of the design of existing MD eyedroppers. The benefits the new application gesture can bring to patients is clear, and patients are keen to change from existing MD eyedroppers – which are far too complicated to use – to the more user-friendly design of the new MD eye bottle. Importantly, the new design does not create any new risks for patients and uses proven technologies compatible with regulatory and economic requirements.

ABOUT THE COMPANY

Akrivision Technologies is a start-up company developing a new concept for an MD ophthalmic dispenser (OD), which has an original design that allows the patient to apply a single, well-calibrated eye drop at a time, safely, easily and accurately, to the conjunctival fold of the treated eye. With a patient-centric approach, the design of the new MD OD allows the patient to replace the difficult and unsecure administration procedure with a safe application procedure that does not require patients to recline their head backwards to administer their eye drops. By improving the experience and satisfaction of patients with their eye drop treatments, the new MD OD has the potential to contribute to the resolution of issues associated with poor compliance and better protect patients' eye health and vision.

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ABOUT THE AUTHORS

Philippe Daull, PhD, Co-Founder and Chief Executive Officer of Akrivision Technologies, holds an MSc in chemistry and biology from the University of Strasbourg, France, and a PhD in cell biology from the University of Sherbrooke, QC, Canada. Dr Daull has over 20 years of industry experience, developing ophthalmic drugs and medical devices for the treatment of anterior and posterior eye segment pathologies (dry eye, glaucoma, macular oedema, diabetic retinopathy). He is experienced in drug development process, from early-stage preclinical studies to translational research, in the preparation of regulatory documents for IND, IMPD, MAA and CE-marked dossiers, and at interacting with regulatory agencies (pre-IND, scientific advice meetings, etc). Dr Daull is the co-author of over 40 peer-reviewed scientific articles, book chapters and is the co-inventor of multiple patents.

Pierre Roy is a Senior Engineer in plastic technology with over 35 years in the medical device industry. Co-Founder and Chief Technology Officer of Akrivision Technologies, he has led and delivered projects across a wide range of medical fields, including ophthalmology and vascular conditions. He has developed many medical devices in anaesthesia, neonatology, ocular drug delivery and diagnosis, as an inventor or co-inventor of more than 25 patents on medical devices. Previously, he was Technical Director of Vygon, a manufacturer of catheters, Chief Technology Officer and Chief Executive Officer of Eyegate Pharmaceuticals, developing an ocular drug delivery device, Founder of Hexamed, providing medical device design and development, consulting services and project management, and Founder and Chief Executive Officer of OPIA Technologies, developing and marketing proprietary diagnosis medical devices for ophthalmology.

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LISTENING TO THE PATIENT'S VOICE TO IMPROVE EYE CARE

In this article, Zoë Davidson, Global Category Marketing Manager – Ophthalmic, at Nemera, discusses the benefits of collaborating with patients to improve eye care management.

Growth in the global ophthalmic eyedropper market is expected to be driven by the increasing prevalence of eye diseases and disorders such as glaucoma, dry eye disease and age-related macular degeneration. Moreover, ageing populations are further propelling market growth due to a higher incidence of age-related eye conditions.[1]

Glaucoma, which is the leading cause of irreversible blindness worldwide, refers to a group of optic neuropathies characterised by the progressive degeneration of retinal ganglion cells. Open-angle glaucoma is the most common form of glaucoma, carrying a chronic prognosis and making up 75–95% of primary cases.[2] Angle-closure glaucoma can be either acute or chronic, but typically has a faster progression than open-angle glaucoma and, therefore, requires more drastic interventions. These two main forms often require the use of eye drops to reduce intraocular pressure and prevent further damage. With the ageing population, the demand for glaucoma medications administered via eyedroppers is also expected to increase, thereby driving market growth. For example, people are six times more likely to develop glaucoma after the age of 60.[3]

The dry eye segment dominated the ophthalmic market in terms of revenue in 2023, owing to its rising prevalence.[1] The definition of a dry eye, according to the Tear Film and Ocular Surface Society Dry Eye Workshop II, is: "Dry Eye is a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiologic roles".[4]

> "Drug delivery device designers and manufacturers must strive not only to understand but to provide solutions for patients encountering administration challenges and to improve at-home eye care management."

One increasingly common extrinsic risk factor for dry eye is digital screen use (e.g. computer, laptop, tablet and smartphone use), which is thought to contribute to its development by affecting blinking dynamics.[5] Other factors contributing to dry eye include ageing, air pollution and hormonal changes. Eye drops or artificial tears are the primary treatment options for alleviating symptoms by lubricating the eyes and providing moisture.[1]

Given the growing ophthalmic eyedroppers market – owing largely to the increase in the ageing population – drug delivery device designers and manufacturers must strive not only to understand but to provide solutions for patients encountering administration challenges and improve at-home eye care management. One way of gaining insight into the patient journey is via testimonials and reviews of real patients using existing products on the market.

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

ACKOWLEDGING PATIENT PAIN POINTS TO IMPROVE EYE CARE MANAGEMENT

As patients become increasingly informed and discerning, they come to rely heavily on the experiences and opinions of others to make well-informed choices. A key advantage the strong position Nemera's Novelia® holds as a leading multidose eyedropper for preservative-free (PF) formulations is having access to a cornucopia of verified patient reviews on e-commerce websites and social media platforms. This is especially true for over-the counter products for the treatment of dry eye.

Products on the market using the Novelia® device consistently rate highly among patients. For example, Systane™ complete PF multidose dry eye drops have maintained an average star rating of 4.5/5, across over 10,000 verified customer reviews since its market launch in 2022, making it the number one product in the moisturising eye drops category on Amazon US (Figure 1).

Online reviews by patients are an invaluable asset for Nemera, providing insights into real patient experiences. Even less-than-positive aspects offer valuable feedback for improvement that Nemera embraces as an opportunity to identify weaknesses and make meaningful improvements to its products and services.

Preservative-Free

The majority of eye drops today contain preservatives to maintain the sterility of eye drop formulations. The most commonly used preservative is benzalkonium chloride, which has been known to damage the cornea with long-term use.

Preservatives can also cause allergies or ocular irritation, and some can even cause a toxic response.[6] Any such reactions are issues for patients who rely on the long-term use of eye drops for chronic conditions.

Control

Patients and healthcare professionals alike desire a bottle that allows patients to control the number of drops by consistently delivering a single drop with each actuation. A study of glaucoma patients found that 90% used an erroneous technique, with many patients missing the eye entirely.[7]

Novelia's PureFlow™ technology not only serves as a venting system but also controls medication flow (Figure 2). Nemera has adapted the flow control within Novelia® to avoid multiple drop delivery into the eye and ensure that only one calibrated drop is dispensed at a time. Specifically, Nemera offers three different PureFlow™ versions, each tailored to formulations of differing viscosities, from highly fluid to highly viscous. In addition, five different valve sizes are available, each one delivering a different calibrated drop size. This allows Nemera's team 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 1: Systane™ hydration PF multidose lubricant eye drops for the treatment of dry eye launched in the US market in 2021 with Novelia® (image courtesy of Alcon).

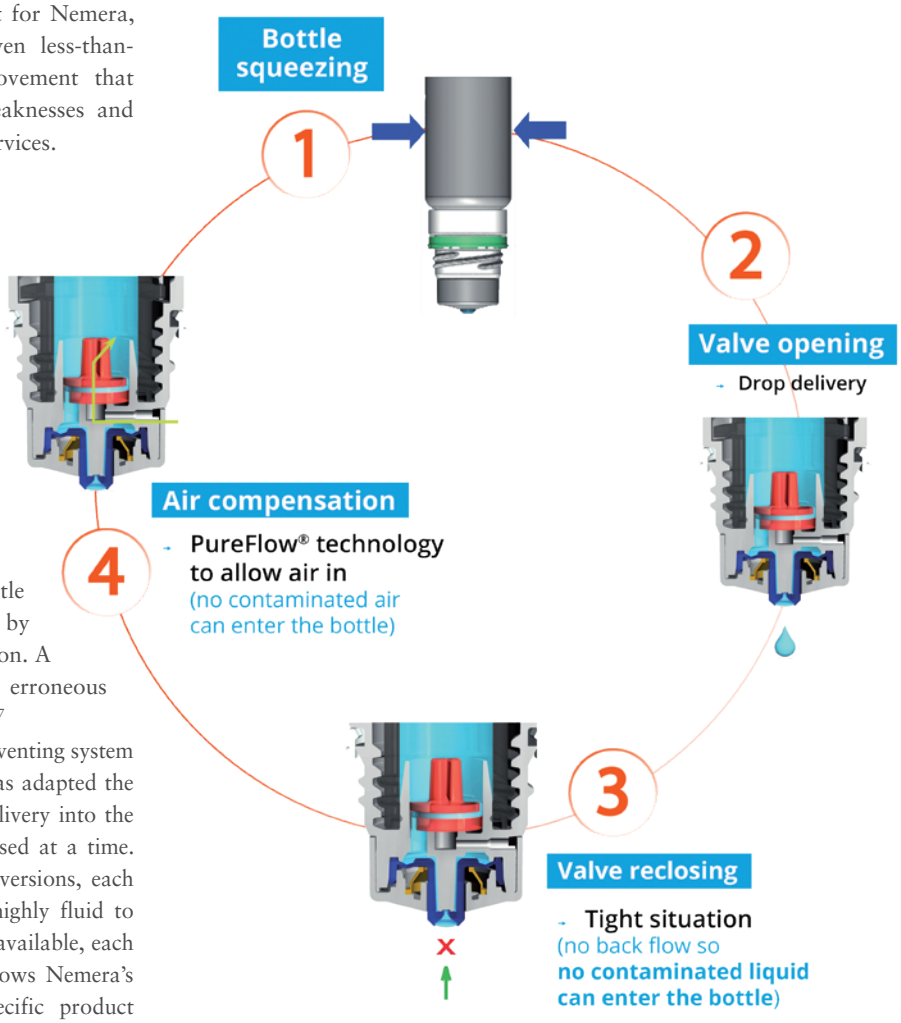

Figure 2: The Novelia® system uses a non-return valve that removes the need to filter the liquid.

Ease of Use

Patients, even those with dexterity issues and tremors or shaking, must be able to manipulate the delivery system effectively and administer a single drop. Contributing factors to the preference for Novelia® by 76% of patients included the intuitiveness of the screw-on cap and the associated reassurance and squeeze force required towards the product's end of life. Novelia® required only 6% more pressure to squeeze the bottle at the end of the treatment compared with at the beginning, whereas for other PF multidose bottles, the increase in required pressure was 35%.[8]

For example, one verified Amazon US customer, in her review of Systane™ hydration PF, said: "*So delighted with this packaging. Have used a competitor's product and I had to use 2 hands to squeeze the bottle. (I am 83 with very little grip strength.) This bottle is much softer, and I am able to use 1 hand which easily leaves my other hand free to 'open' my lower lid and instil the drops in the appropriate way. I don't care for the individual PF drop containers as they are more expensive when using throughout the day and I found those containers were also difficult to squeeze.*"

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. One verified customer on Feefo UK (Butterflies Eyecare), in her review of Evolve SOOTHE & RENEW eye drops 10 mL, said: "The blue dot on the dispenser helps line up the bottle with the eye. Because I can see how far away the bottle is from my eye, I am less threatened by it than a pointed dispenser. Thus, I can relax more when applying drops to my eyes (whether I do it or someone else does). This makes the application process a lot easier."

Transparency

Patients need more visibility into their medication supply, so that 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, 7.5, 11 and 15 mL). All sizes are available in low-density polyethylene (LDPE) either in white or natural (transparent), allowing patients to know when their medication is running low. Nemera has also developed a polypropylene (PP) 11 mL bottle for specific formulation compatibility (Figure 3). Novelia® bottles have been validated using both gamma and ethylene oxide sterilisation.

Portability

A patient must be able to easily transport their medication; for dry-eye syndrome 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. Other marketed devices that use a snap-on cap have been found by patients to be less robust, with several instances of leaking during transport, whether 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 5 for the three features.[9] One verified Amazon customer said: "*Love the portability. It's nice not needing to carry around small individual containers for each use in your pocket and around the house. I do like that this one (as) you can twist the cap on and off (so it) feels more secured.*"

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

Figure 3: A full range of LDPE bottles is available in 5, 7.5, 11 and 15 mL, as well as 11 mL PP.

Sustainability

Patients also report concerns regarding unit doses. These include cost (as more packaging and eye drop solution per dose is required), waste and convenience, as it is easier to store a multiuse bottle in a preferred location than to ensure that the patient has the correct number of unit dose pipettes with them every day.[10]

Handling difficulties have been noted with unit doses and their use by older patients, and inappropriate finger manipulation could be associated with an increased risk of contamination.[11] Due in part to the rapidly ageing population, the number of people with glaucoma worldwide is expected to increase to over 111 million by 2040.[12]

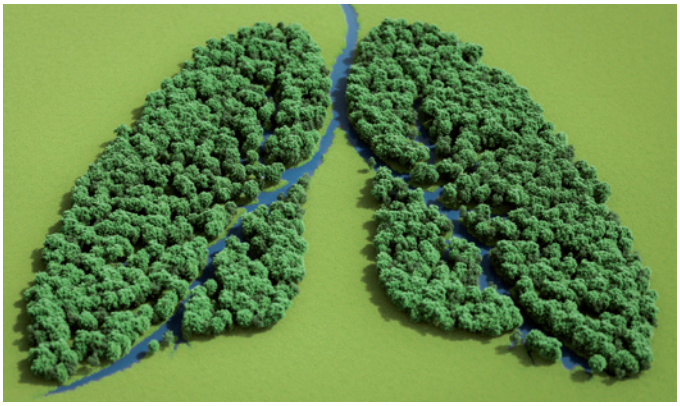

Figure 4: Reducing carbon emissions.

Figure 5: Nemera has doubled its Novelia® production capacity by creating two additional assembly lines in their US site, (Buffalo Grove, IL).

In an analysis conducted by Nemera, comparing Novelia® multidose eyedropper with unit dose packaging for a glaucoma-type regimen (one drop per eye twice per day) over one month, there was eight times less plastic used, 25 times less drug waste and nine times less energy needed for transportation for Novelia®, compared with a unit dose.[13]

In 2021, Nemera decided to subscribe to the Science-Based Target initiative (SBTi) to define and develop best practices for carbon reduction. One of the first objectives is to reduce the company's Scope 1 and 2 emissions by 90% by 2030 from a 2019 base year. In addition, since February 1, 2024, the manufacturing facility in La Verpillière, France, where Novelia® is manufactured has been certified ISCC PLUS. This certification scheme for bio-based, renewable and circular raw materials reinforces Nemera's implementation of sustainability goals (Figure 4).

SUPPORTING CUSTOMERS TO SUPPORT PATIENT NEEDS WORLDWIDE

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

Nemera's regulatory team is on hand to support customers with their submission filings, providing guidance on supportive documents for registration. Nemera can also assist customers in finding the right ready-to-go dossier available for private labelling of certain molecules with the Novelia® delivery system. Nemera has a substantial list of partners, formulation licensors and fillers, all working in collaboration to bring to customers a finished drug-device combination product with Novelia®.

"Nemera's regulatory team is on hand to support customers with their submission filings, providing guidance on supportive documents for registration."

While user-friendly containers are important, educational resources that teach patients how to apply their eye drops correctly have been found to mitigate issues with unintentional non-compliance.[14] For example, Nemera can support customers with product market launch, in educating sales teams and healthcare professionals on the delivery device, dedicated training and materials to assist in promotional material creation. Customisable patient guidance videos are also available in several languages to increase patient compliance around the world.

Currently, Novelia® has approximately 300 references on the market for prescription and over-the-counter products in over 55 countries across Europe, Latin America, North America, Oceania, the Middle East and Asia Pacific.

To serve customers in supporting patient needs, Nemera has extended its manufacturing capabilities in the US, and in so doing has doubled its capacity to produce Novelia® PF multidose eyedroppers (Figure 5).

ABOUT THE COMPANY

As a world-leading drug delivery device 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 with their combination products. 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 AUTHOR

Zoë Davidson has held the position of Global Category Marketing Manager for Nemera's ophthalmic franchise since 2019. In this role, Mrs Davidson is responsible for the strategy management of Nemera's flagship Own-IP multidose eyedropper for preservative-free formulations, Novelia®. With over seven years' experience in the pharmaceutical and medical device industry, Mrs Davidson is motivated about gaining insights into patients' needs and wants within the ophthalmic space.

ONdrugDELIVERY

2024/25 EDITORIAL CALENDAR

Publication Month	Issue Topic
April	Pulmonary & Nasal Drug Delivery
Apr/May	Drug Delivery & Environmental Sustainability
May	Delivering Injectables: Devices & Formulations
May/Jun	Oral Drug Delivery
June	Connecting Drug Delivery
Jun/Jul	Industrialising Drug Delivery
September	Wearable Injectors
Sep/Oct	Drug Delivery & Environmental Sustainability
October	Prefilled Syringes & Injection Devices
November	Pulmonary & Nasal Drug Delivery
December	Connecting Drug Delivery
January 2025	Prefilled Syringes & Injection Devices
February	Skin Drug Delivery: Dermal, Transdermal & Microneedles
March	Ophthalmic Drug Delivery

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COMPARATIVE USABILITY STUDY OF MULTIDOSE PRESERVATIVE-FREE EYE DROP DEVICES

In this article, Rouven Kraus, Head of Sales at Aero Pump, discusses the results of a study investigating dose accuracy and reproducibility, along with user preferences, for a variety of multidose preservative-free eye drop devices.

INTRODUCTION

The administration of ophthalmic drugs presents a multifactorial challenge for numerous patients suffering from dry eye disease, glaucoma or any other ophthalmic-associated disease that requires the use of topical eye drops. Non-adherence to prescribed medication regimens can occur unintentionally when medication is not administered correctly.[1] In the dry eye field, with medications such as sodium hyaluronate to relieve eye dryness and soreness, unintentional non-adherence can be avoided by simply dispensing an additional eye drop, even if this results in a more costly approach for the patient. In glaucoma therapies, however, non-adherence poses a more significant concern. These kinds of medications are classified as a drug product with stricter regulations in regard to compliance.

> "Non-adherence to prescribed medication regimens can occur unintentionally when medication is not administered correctly."

STUDY OBJECTIVE

The independent medical usability agency, Custom Medical (Darmstadt, Germany), performed a comparative usability study with several commercialised eye drop devices using multidose preservative-free technologies (MDPF). Custom Medical is a well-known agency certified by ISO 13485, offering EU Medical Device Regulation (MDR)- and US FDA-compliant usability and human factors engineering studies and user interface design. For this study, the emphasis was placed on evaluating dose accuracy and reproducibility among the tested devices. The study involved a multinational benchmark assessment with lay persons possessing either US or European citizenships.

METHODOLOGY

The study included four MDPF eye drop devices from different manufacturers – the 3K®-Pump Eye Dropper with Standard and ComfortGrip finger sleeves from Aero Pump, the Ophthalmic Squeeze Dispenser (OSD) from Aptar Pharma (IL, US), and Novelia® from Nemera (Lyon, France). The participants, who were evenly distributed between the US and Europe, were predominantly female and represented diverse age groups, and engaged in two tasks per test device. The tasks simulated scenarios of first use and repeated use, focusing on the precise dispensing of one drop onto protective goggles and targeted surfaces.

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#	Device name	Accessory	Manufacturer
1	3K®-Pump Eye Dropper	Standard (cylindric) finger sleeve	Aero Pump
2	3K®-Pump Eye Dropper	ComfortGrip finger sleeve	Aero Pump
3	OSD	–	Aptar Pharma
4	Novelia®	–	Nemera

Table 1: Test devices.

TEST DEVICES

Testing included a total of eight different types of MDPF eye drop devices, of which five were based on different designs of Aero Pump's 3K®-Pump Eye Dropper. The focus of this study lay on the four MDPF devices described in Table 1.

PARTICIPANT DEMOGRAPHICS

US Citizens

- 50% male/50% female

- 10% aged 20–45 years
- 30% aged 46–60 years
- 60% aged 61+ years

EU Citizens

- 30% male/70% female

- 20% aged 20–45 years
- 30% aged 46–60 years
- 50% aged 61+ years

According to demographic statistics, the majority of ophthalmic disorders are more prevalent in older individuals and tend to affect women more frequently than men.[2] These gender and age factors were considered when selecting the subject group for this comparison study.

The entire study was monitored by qualified persons, who posed specific tasks and questions to the lay person participants. Eight questions were posed in total, two of which have not been included in the final statistics. The focus of the six included questions was to gather data on the participant's preferences for the different MDPF eye drop devices tested.

"The majority of ophthalmic disorders are more prevalent in older individuals and tend to affect women more frequently than men."

RESULTS

The study evaluated the participants' experiences and preferences using a 10-step scale across six questions addressing various aspects of device usability. Overall, the 3K®-Pump Eye Dropper with ComfortGrip finger sleeve received the highest ratings.

Simulation of First Use and Repeated Use Scenarios

The target of the test was for participants to precisely dispense one drop from the test devices in two differing scenarios. For the first task, participants were tasked to drip exactly one drop onto the right side of a pair of worn safety goggles and one drop on the left side of the goggles (Figure 1). For compliance reasons, the participants did not have to dispense the drops into their eyes, but onto the worn protective goggles.

For the second task, participants were asked to drip exactly one drop into each of the eight circles on a target surface (Figure 2). The target surfaces were based on 2 cm-sized round circles to represent the size of a human eye. This test was designed to determine the dose accuracy of the devices.

Figure 1: Dispensing onto eye/protective goggles.

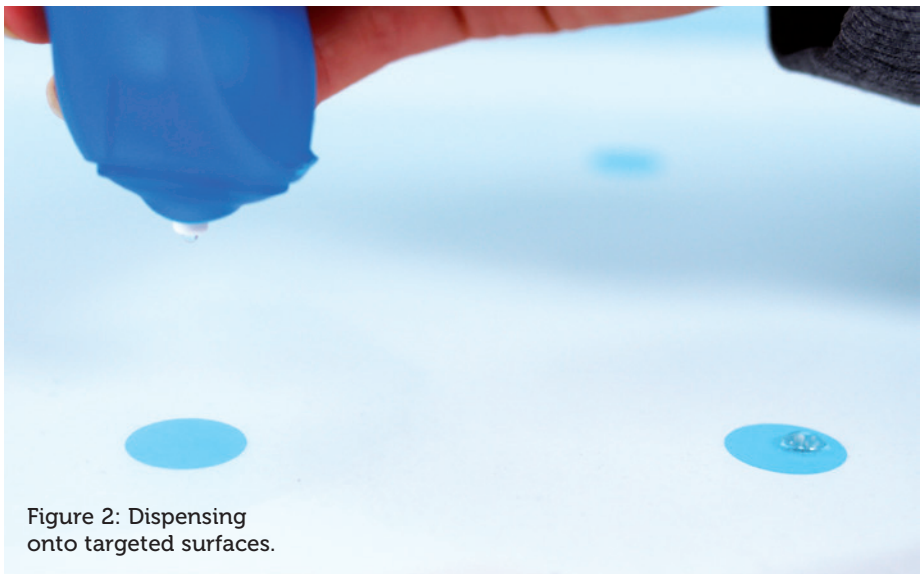

Figure 2: Dispensing onto targeted surfaces.

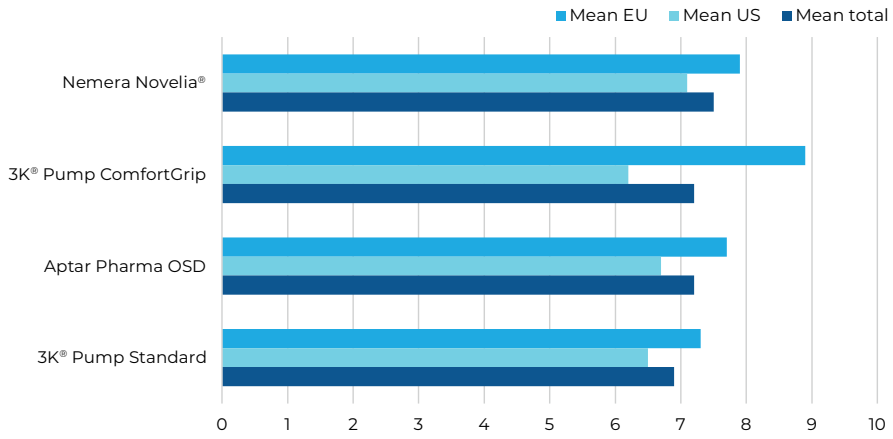

Figure 3: Result for "How easy or difficult was it for you to apply the drops exactly into your eye or safety goggles?"

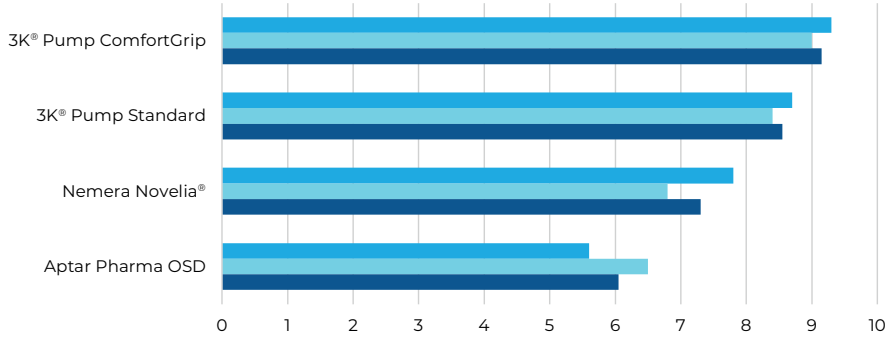

Figure 4: Result for "How easy or difficult was it for you to dispense precisely one drop for all applications?"

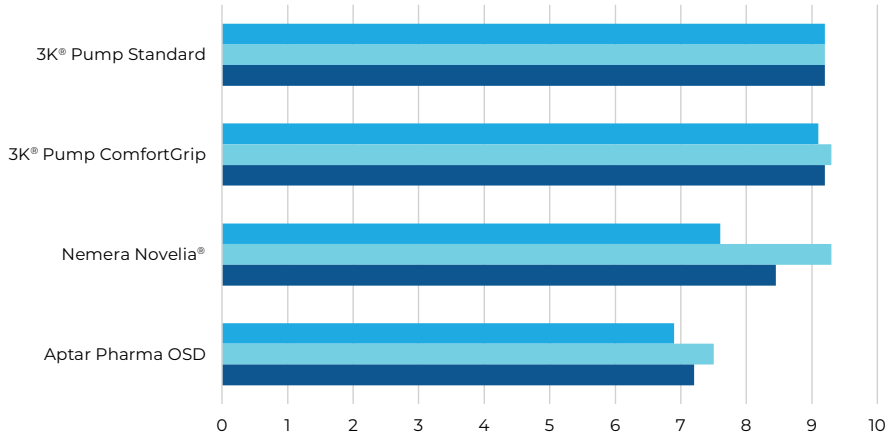

Figure 5: Result for "How consistent did you find the size of the drops?"

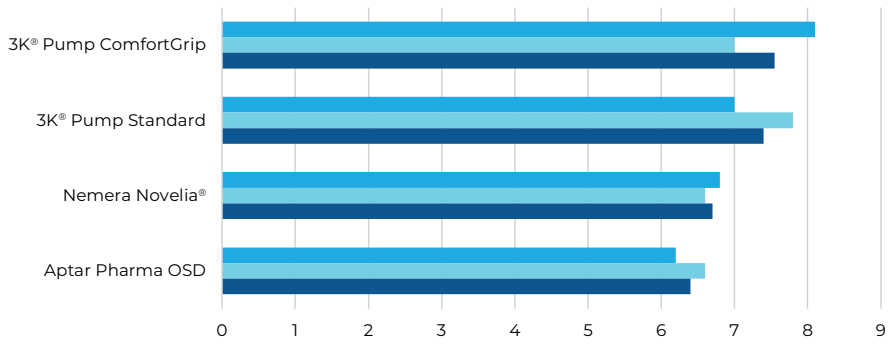

Figure 6: Result for "How high do you consider the risk of incorrect use of this dropper to be?"

Tasks and Questions

The following questions were rated on a 10-step scale:

Q1: *"How easy or difficult was it for you to apply the drops exactly into your eye or safety goggles?"*

Question one was focused on the dose accuracy of the dispensing system. The US participants found Novelia® to be most exact, while the EU participants preferred the 3K®-Pump with ComfortGrip finger sleeve (Figure 3).

Q2: *"How easy or difficult was it for you to dispense precisely one drop for all applications?"*

Question two was focused on the dose control, ensuring that just one single drop was dispensed per activation. The 3K®-Pumps were ranked by far the best (Figure 4).

Q3: *"How consistent did you find the size of the drops?"*

Question three assessed dose consistency, which is strictly regulated by pharmacopeial guidelines. In this study, the 3K®-Pumps were perceived to create the most consistent drops overall (Figure 5).

Q4: *"How high do you consider the risk of incorrect use of this dropper to be?"*

Question four was focused on safety – risk assessment is also a key factor for patients to choose the right product for them. The 3K®-Pumps were perceived to be the most safe (Figure 6).

Q5: *"How well does the dropper fit in your hand?"*

Question five considered usability based on the test devices' sizes and forms. In this study, the average participant said that the squeeze-type devices fitted better in their hands. However, there was a clear preference of the EU participants towards the 3K®-Pump with the ComfortGrip finger sleeve (Figure 7).

Q6: *"How do you like the product's appearance?"*

Question six focused on the test devices' aesthetics. The OSD's appearance was preferred by all participant groups, followed by the 3K®-Pump with ComfortGrip sleeve (Figure 8).

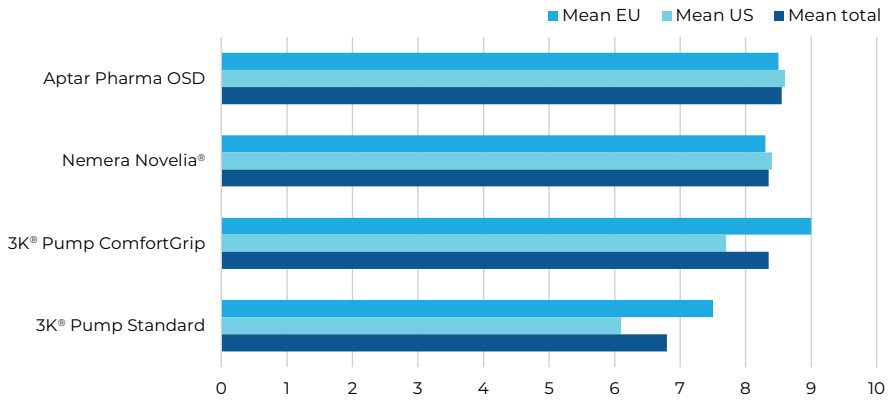

Figure 7: Result for "How well does the dropper fit in your hand?"

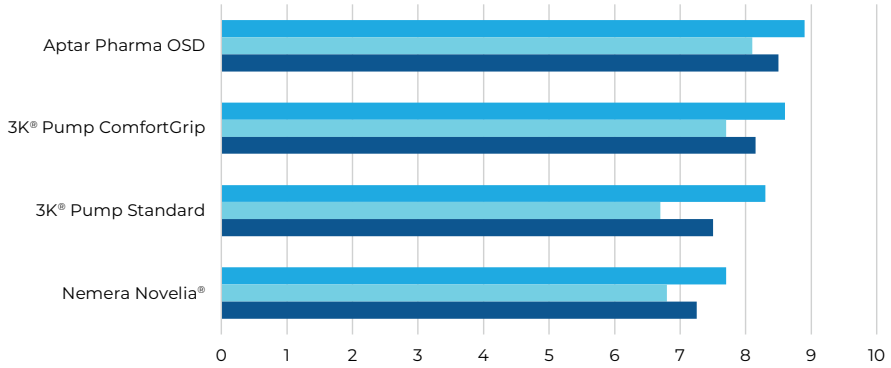

Figure 8: Result for "How do you like the product's appearance?"

	3K® ComfortGrip	3K® Standard	Novelia®	OSD
Q1	7.2	6.9	7.5	7.2
Q2	9.2	8.6	7.3	6.1
Q3	9.2	9.2	8.5	7.2
Q4	7.6	7.4	6.7	6.4
Q5	8.4	6.8	8.4	8.6
Q6	8.2	7.5	7.3	8.5
Mean	8.3	7.7	7.6	7.3

Table 2: Overall rating.

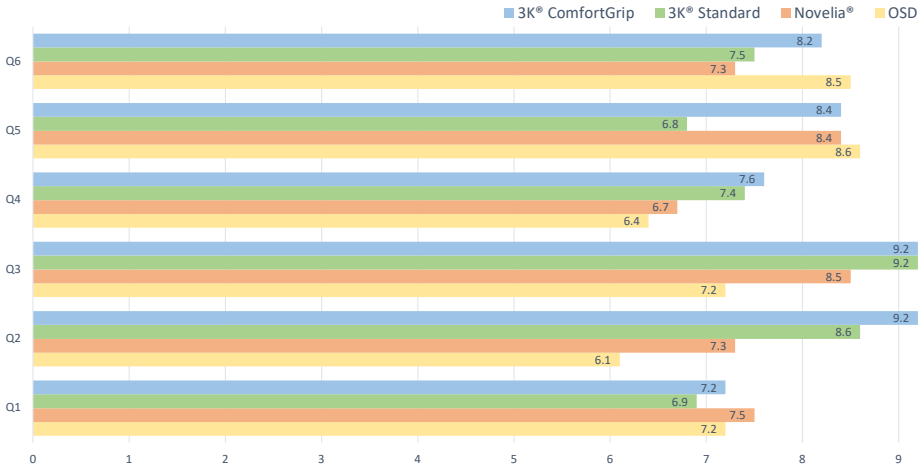

Figure 9: Overall rating.

> "Widely used for both over-the-counter and prescription medications, the 3K®-Pump is an established and trusted choice for ophthalmic medications."

Taking all these results into consideration by compiling the ratings of all six questions (Table 2), the 3K®-Pump with ComfortGrip finger sleeve received the best overall rating, followed by the 3K®-Pump with Standard finger sleeve (Figure 9).

The final question posed to the participants asked them to come to a conclusion on which of the test devices they thought would minimise the risk of overdosing. The majority of the participants preferred a metered dose pump over a squeeze dispenser (Figure 10).

CONCLUSION

This study's findings underscore the importance of taking usability factors into account when designing eye drop devices, particularly for ensuring dose accuracy and user preference. The study highlighted the potential of metered dose pump devices, such as Aero Pump's 3K®-Pump, to enhance patient adherence and satisfaction in ophthalmic medication administration.

AERO PUMP'S PRESERVATIVE-FREE OPHTHALMIC MULTIDOSE SYSTEM

Aero Pump's 3K®-Pump Eye Dropper has become well-established on the market since its first product launch in 2006. It is the only available eyedropper based on a purely mechanic pump technology that offers a metered dose. The 3K® System incorporates specialised components that actively avoid microbial ingress, ensuring microbiological safety. Widely used for both over-the-counter and prescription medications, the 3K®-Pump is an established and trusted choice for ophthalmic medications.

With a focus on user convenience, the 3K® System offers various user-friendly actuation aids to facilitate effortless application directly into the patient's eye. Pharmaceutical manufacturers can choose their preferred finger sleeve design, which can be customised according to the needs of the end user (Figure 11).

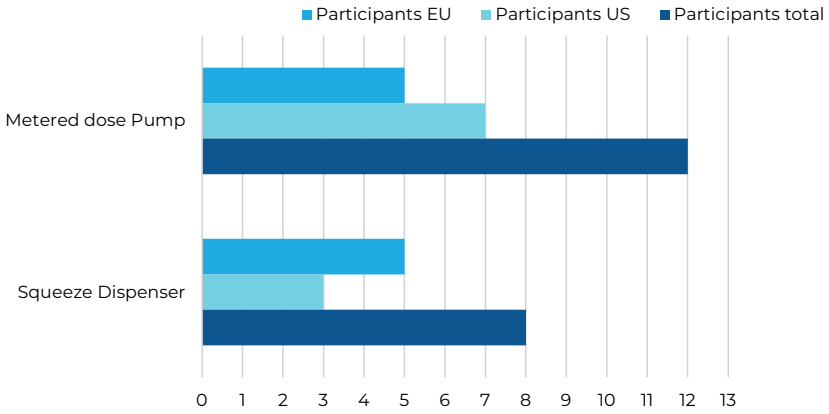

Figure 10: Risk of overdosing, select one particular device.

Figure 11: Aero Pump's ophthalmic multidose system in different sleeve designs.

Flexible in its compatibility, the pump system can be adapted for use with both plastic and glass containers and can accommodate various fill sizes. This versatility minimises interactions between the packaging materials and the drug substance, offering distinct advantages.

Maintaining precision throughout its lifecycle, the 3K® System dispenses an accurate dose with each stroke, providing consistent performance. The actuation force of Aero Pump's ophthalmic multidose system remains stable regardless of the residual liquid inside the container.

For drug-device combination products, Aero Pump can provide a CE-marked product as a medical device compliant with the EU MDR. This facilitates and expedites the approval process for the finished drug product, and further avoids additional costs for a notified body opinion. Aero Pump offers comprehensive support for a successful regulatory submission process in markets worldwide.

ABOUT THE COMPANY

Aero Pump GmbH is a leading manufacturer of high-precision application systems for the pharmaceutical and healthcare industry, focused on innovation, multi-functionality and contemporary design. The company's spray pumps and dropper systems are widely established in markets worldwide; primarily used in ophthalmic, respiratory and dermal fields; and suitable for both preserved and preservative-free over-the-counter and prescription drugs. The company has extensive knowledge in supporting pharmaceutical customers with custom-fit regulatory files for a successful submission.

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ABOUT THE AUTHOR

Rouven Kraus has more than 10 years of experience in the drug delivery market. He started his career in sales for a domestic iron foundry in Mainz, Germany, and joined Aero Pump in 2012 to augment the sales of its drug delivery device portfolio. In his role as Head of Sales, he manages global sales as well as the company's strategic approach to new developments and delivery technologies.

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UNITHER PHARMACEUTICALS' INNOVATIVE APPROACH TO OPHTHALMIC MANUFACTURING

In this interview, Natalia Servol shares insights into Unither Pharmaceutical's preservative-free multidose technology. With a focus on addressing patient needs and meeting industry demands, Unither Pharmaceuticals offers a distinctive approach to sterile manufacturing in the ophthalmic sector.

NATALIA SERVOL, UNITHER PHARMACEUTICALS

Natalia Servol holds a double master's degree in international business and education, and has more than 12 years' experience in the health industry. Her experience with brands such as Babymoov (Clermont-Ferrand, France) and Laboratoire TVM (part of the Dômes Pharma Group, Pont-du-Château, France) gives her a 360-degree understanding of the health and care sector in her role as Head of Ophthalmic Business at Unither Pharmaceuticals. Here, Ms Servol speaks about the company's equipment for compounding and fill-finish of preservative-free products into multidose bottles, part of Unither's unique and innovative preservative-free multidose offering for partners.

Q What technologies does Unither offer for ophthalmic products?

A Unither's industrial engineering offers three main technologies for sterile manufacturing of ophthalmic products: blow-fill-seal (BFS) in single-unit vials, preservative-free multidose (PFMD) filling and common multidose (MD) filling for products with preservatives.

We are always looking for innovative solutions to meet our customers' requirements and we're always aware that, ultimately, this equates to meeting patients' needs. By building industrial synergy between the two main technologies for preservative-free ophthalmic products, BFS and PFMD, we believe we're truly providing our customers with tailored, sustainable solutions, and patients with products that will enhance their quality of life. This has been the driving force behind the creation and realisation of an innovative PFMD manufacturing line.

> "By creating a synergy with unit-dose vials, the PFMD presentation acts as a complement to BFS technology and gives patients continual security and product quality throughout the treatment period."

Q Can you tell us more about the PFMD line?

A We are proud and delighted with our cutting-edge PFMD line, which is an embodiment of more than 30 years of sterile know-how. It represents uncountable hours of teamwork with external suppliers and customers (Figure 1).

By creating a synergy with unit-dose vials, the PFMD presentation acts as a complement to BFS technology and gives patients continual security and product quality throughout the treatment period.

The PFMD product is manufactured by aseptic processing. Aseptic manufacturing and the sterile fill-finish process, in which the drug product, container and closure/cap are first subjected to separate sterilisation methods – appropriate to each component and its requirements – and then brought together by the isolator machine.

Q How did you develop this process?

A The PFMD line at Unither is the result of an idea, customer feedback and demands to meet patient needs. As of today, we work with technologies from two major companies in the ophthalmic industry: Aptar Pharma (Crystal Lake, IL, US) and Nemera (Lyon, France). However, our patient-oriented philosophy means that new tailored solutions will be added to our offering in the near future.

Q How do you respond to customers' needs?

A Every one of our manufacturing plants (in France, the US, Brazil and China) has a dedicated R&D team and pilot workshop for internal development and customer projects. If required, some works can be provided by or executed with the participation of our innovation and development centre in Bordeaux (France), or the back-up manufacturing plant. Our customers benefit from the R&D and international industrial footprint of Unither, from early-stage work to commercial manufacturing.

We answer and meet all relevant international quality and regulatory

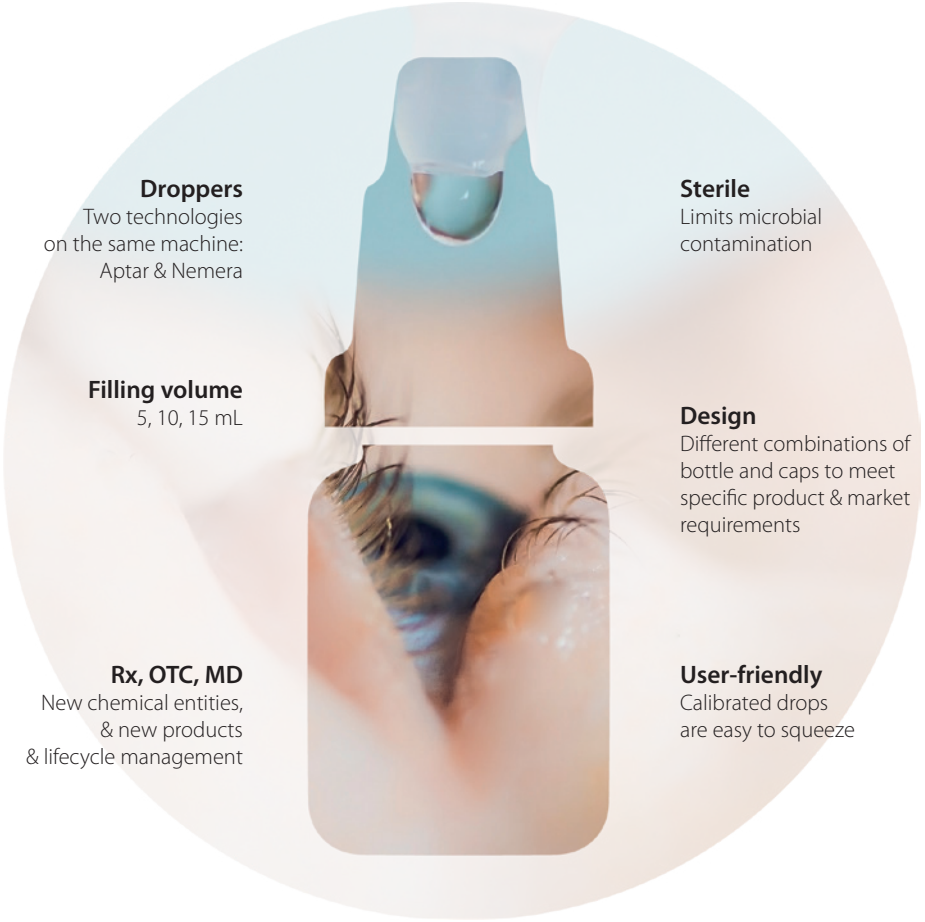

Figure 1: Unither's innovative PFMD manufacturing line is the embodiment of 30 years of know-how.

standards – are approved by the EMA, US FDA, the ANVISA (Brazil), MFDS (Korea), MoH (China) and many others.

> "Our R&D site in Bordeaux has made a strategic move and the whole team is working hard to turn our Bordeaux site into an R&D Centre of Excellence for Ophthalmology."

We work in an international environment, both for transversal project management and commercial supply.

Q What is next in line for Unither?

A Plenty of exciting projects! Our R&D site in Bordeaux has made a strategic move and the whole team is working hard to turn our Bordeaux site into an R&D Centre of Excellence for Ophthalmology. We keep creating innovative solutions together with our partners. Among many exciting developments, we'd like to mention Curecall (Paris, France), a start-up that specialises in the monitoring of chronic ocular diseases – a user-friendly solution for doctors and patients.

We foresee great challenges in the ophthalmic field and believe that vision science can overcome them by the collaboration and free sharing of ideas within interdisciplinary teams. Our philosophy is to always be open minded.

We will be delighted to discuss these ideas at the ARVO annual meeting and other specialised events.

ABOUT THE COMPANY

Unither Pharmaceuticals is a pharmaceutical subcontractor specialising in the development and manufacturing of single-dose liquid formulations, including eye drops, saline solutions and asthma medications in BFS single doses and liquid stick-packs, for originator pharmaceutical companies and generics manufacturers. Currently employing more than 2,200 people in eight manufacturing plants in France, the US, Brazil and China, Unither Pharmaceuticals recorded sales of €475 million (£406 million) in 2023.

UNITHER PHARMACEUTICALS

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Ophthalmic Product Development

by Unither Pharmaceuticals

PREFORMULATION STUDY

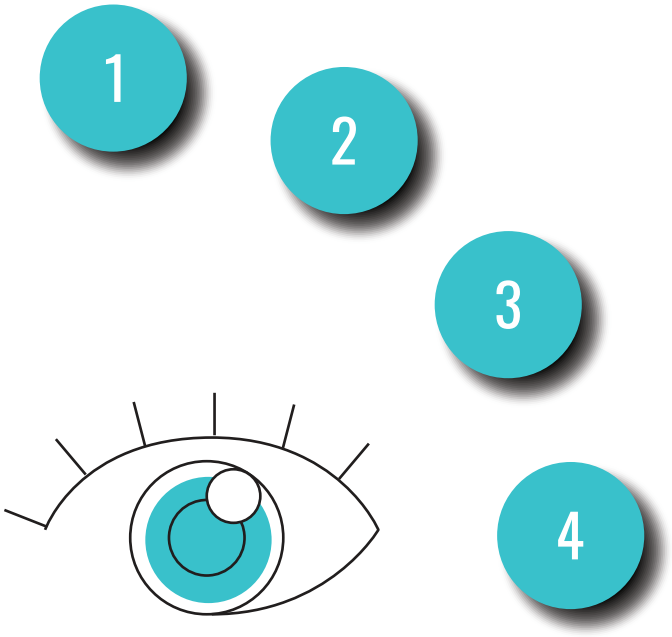
- API characterization: Optical microscopy, assays, DRX, PSD, Log P, Log D, membrane permeability…
- Compatibility study
- Solubility study:
  - Solubility at saturation in different media
  - Solubility improvement: Cyclodextrin complexation, co-solvent, surfactants, micronization…
  - Modelization (software)
  - Early conservation study
- Preclinical batches manufacturing

ANALYTICAL METHODS DEVELOPMENT

- API assay
- Impurities assay and forced degradation study
- Preservative and antioxidant assays if necessary
- Sterility and microbiological controls

FORMULATION STUDY

- Different forms: Solution, Gel, Emulsion, Micellar solution, Micro and nanoemulsion, Nanosuspension
- Formulation development by QBD (risk analysis and DoE on Jmp software)
- Rheology (viscoelastic behavior, gelation assessment, resistance under simulated eye blinking, viscosity behavior after tear contact...)
- Bioadhesion (mucoadhesive force)
- PSD by laser diffraction and DLS, Zeta potential if necessary
- Packaging choice: single or multiple use, glass or plastic
- Finished product characterization: Appearance, pH, Osmolality, Density, Drop size, Viscosity



DEVELOPMENT CYCLE

STERILIZATION STUDY

- Steam sterilization impact
- Filtration study
- Filterability study

CONTAINER/CONTENTS INTERACTIONS

- Stressed studies
- Extractables and leachables (support of packaging supplier)

SCALE-UP STUDY

- Process robustness evaluation by QBD (risk analysis and DoE on Jmp software)
- Preliminary stability study
- Technical batches
- Analytical methods validation
- Clinical batches manufacturing

INDUSTRIALIZATION

- Small commercial batches
- Process validation
- ICH stability studies and on going stability studies

UNITHER PHARMACEUTICALS

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ADDRESSING INTRAVITREAL PRODUCT MANUFACTURING AND DEVELOPMENT CHALLENGES

Here, Andrea Allmendinger, PhD, Chief Scientific Officer, Hanns-Christian Mahler, PhD, Chief Enablement Officer, and Philipp Behrendt, PhD, Quality Assurance Manager, all at ten23 health, discuss the challenges of filling very small volumes into syringes for intravitreal injections, and how ten23's innovative filling technology can help combat the critical issue of air bubble formation.

Previously in ONdrugDelivery, ten23 health has discussed the need for a profound, holistic understanding of product and manufacturing processes, both current and emerging, as well as regulatory and quality requirements for intravitreal (IVT) applications; the need for cutting-edge manufacturing technologies; and for expertise in the production of ophthalmic products. These elements are crucial for ensuring patient safety, compliance with regulatory standards and minimising costs. In this article, ten23 showcases how the company's aseptic manufacturing services at its innovative and highly adaptable automated, isolator-based good manufacturing practice (GMP) filling line in Visp, Switzerland, effectively address the intricate demands and technical challenges encountered in the development and manufacture of IVT preparations, with a special focus on the filling volume in relation to the injection volume.

"Although there are reports of injection volumes reaching as high as 100 µL, limited information exists regarding the upper limit for injectable volume into the back of the eye."

INJECTION VOLUME AND PRIMARY PACKAGING CONTAINER SELECTION

IVT preparations are typically supplied in a 0.5 mL, or sometimes 1 mL, prefilled syringe configuration, in most cases with a Luer lock. However, IVT applications commonly involve injection volumes ranging from 25 to 50 µL. Although there are reports of injection volumes reaching as high as 100 µL, limited information exists regarding the upper limit for injectable volume into the back of the eye.[1]

Because IVT administration volumes often fall well below the minimum fill volumes achievable by most sterile facilities and contract manufacturing organisations,

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IVT products are often significantly overfilled. As such, the end-user, usually a healthcare professional, may need to manipulate syringes for IVT use by expelling any potential air and liquid formulation to reduce the contents of the syringe down to the target administration volume, made visible with graduation marks, in a practice known as "down-dosing". For instance, syringes filled with a target fill volume of 100 µL may need to be down-dosed to a target injection volume of 50 µL. However, down-dosing presents a precision challenge for users in terms of accuracy, introduces the risk of variability in administered volume and leads to significant API losses – generating substantial product waste, which adversely impacts the overall cost of goods.

The precision of the injection device typically defines the lower limit of the injected volume, and syringes intended for IVT injection must undergo thorough characterisation to ensure dosing accuracy. The lower limit of dosing currently stands at approximately 10 µL for conventional syringes, depending on the graduation marks and the proficiency of the intended users. In particular, the absence of an air bubble in the syringe is highly desirable from a user perspective, as down-dosing may become considerably more challenging if one is present. For injectable products not undergoing down-dosing, the essential absence of any headspace is additionally relevant from a patient safety perspective, as the injection of air is generally undesirable. Furthermore, an air bubble can provide further challenges, such as during air transport or downstream processes using pressure differentials.

Combination products are typically filled in ready-to-use primary packaging containers, such as syringes (Figure 1), often in nest/tub configurations. This implies that the container is delivered pre-washed, pre-sterilised and ready for filling by the supplier. However, this necessitates that device attributes meet the final drug product requirements throughout the supply chain until the filling point. This includes device performance and safety-relevant parameters, ensuring the absence of micro-organisms (maintenance of sterility), compliance to endotoxin limits and prevention of potential contaminants, such as particles.

The introduction of novel containers into the market has increased, requiring a comprehensive characterisation of such primary packaging containers and their compatibility with the product. Essentially, the characterisation of primary components with the final product's quality in mind is crucial. This involves comprehensive assessments, including extractables and leachables testing, container closure integrity and product quality evaluations, such as particle contamination.

Figure 1: Ready-to-use primary packaging containers, such as syringes, are common for combination products.

"The introduction of novel containers into the market has increased, requiring a comprehensive characterisation of such primary packaging containers and their compatibility with the product."

Stability testing of the product filled into primary containers covers various biochemical and pharmacopeial endpoints, addressing critical quality attributes (CQAs) such as content and purity, along with obligatory CQAs, including both sub-visible and visible particulates. In addition, novel containers must be assessed for their manufacturability and whether they reliably deliver a reproducible quality of output. Critical material attributes can often be identified as a result of such manufacturing process assessments.

FILL-FINISH PROCESS – SMALL-VOLUME, BUBBLE-FREE FILLING

From a technical perspective, filling small volumes into primary packaging containers during fill-finish operations is challenging both from an accuracy and a visual inspection perspective. Filling of small volumes well below 1 mL is typically achieved by the selection of adequate filling technologies. While piston pumps have traditionally been believed to be the most suitable technology for achieving high precision, nowadays, very-low-volume positive-displacement pumps, such as peristaltic pumps, are typically preferred over piston-pump systems. Additionally, peristaltic pumps are more compatible with biologics.[2]

Novel pump systems, such as liner peristaltic pumps, which have been suggested to be superior in terms of filling accuracy for small volumes, have not yet become standard in filling systems. Alternative time-pressure systems have drawbacks in terms of filling accuracy, especially at low volumes and for highly viscous products, because of potential air bubble formation and the temperature dependency of the fill volume.

Besides dosing accuracy, the selection of the filling technique depends on numerous parameters, including operational and maintenance considerations, the availability

Figure 2: ten23's facilities include the capability for highly accurate, air-bubble-free filling of very low-volume primary containers in isolators operated in class C.

of the pump system at the manufacturing site and associated investment plans. It is also important to consider the impact of the product of factors – such as the minimisation of interfacial stresses for biological product solutions or wear and tear (including shedding).[2]

Most filling technologies, including peristaltic pump systems, use volumetric dosing based on optimised filling pump parameters that operate within defined alarm and action limits. As a gold standard and to increase filling accuracy, these limits are typically coupled to a feedback loop that measures the fill weight of the individual product by weighing the differential of the product vial pre- and post-fill. In some instances, fill volumes are controlled by weight up to 100%. In other cases, the feedback loop even allows for re-dosing, omitting sole reliance on volumetric methods.

As already discussed, the presence of an air bubble in an IVT syringe may create significant challenges during down-dosing and for dosing accuracy. The challenge persists during air transport, emphasising the importance of the design of the fill volume and allowable headspace in relation to the chosen primary packaging and stopper. Transport conditions may induce stopper movement due to pressure changes, potentially compromising container closure integrity. Movement of the air bubble in the syringe during transport may also cause additional interfacial stress to the product, which can be detrimental for product quality. Furthermore, terminal sterilisation, if affected by pressure changes, may become critical depending on the headspace in the syringe. Therefore, achieving a bubble-free plunger setting at the manufacturing facility, allowing for minimal headspace, may be crucial.

> "High-precision bubble-free and low-volume filling technology is a key asset of ten23, with a combination of appropriate stopper placement techniques and adequate pressure settings."

High-precision bubble-free and low-volume filling technology is a key asset of ten23 (Figure 2), with a combination of appropriate stopper placement techniques and adequate pressure settings. This approach eliminates many challenges observed in slip-stoppering, is applicable for coated stoppers and is preferable for high-viscosity biologics, such as ophthalmic medicines. The advantages of bubble-free filling include high dosing accuracy, as the syringe orientation does not affect the dosage delivery; greater sterility assurance, as there is a much less chance of plunger movement during shipping; better biological stability regarding product headspace interaction; and less chance of needle dripping after needle shield removal.

Besides the challenges associated with accurately filling small volumes, any challenges related to visual inspections are especially apparent with IVT products. Especially in vial configurations, they often feature a meniscus just slightly above the container bottom, making it difficult for visual inspection operators to detect visible particles, especially if solution and formulation present further challenges for visibility, such as opalescence. Small filling volumes are equally difficult for automated visual inspection.

CONCLUSION

ten23 possesses the capability to precisely fill very small volumes for IVT applications based on the company's innovative filling technology, avoiding the presence of an air bubble and minimising product loss. During product development and manufacturing, ten23 fosters the alignment between drug product manufacturing capabilities and the specifications of the device partner and primary packaging supplier to ensure compliance with all agreed parameters.

ABOUT THE COMPANY

As a contract design and manufacturing organisation, ten23 health is appropriately positioned to anticipate and mitigate the technical challenges when developing formulation and manufacturing processes for injection devices. ten23 offers integrated development of formulation services, analytical development and product characterisation, device selection and testing, and drug product process design and characterisation. ten23 also provides fill-finish manufacturing of complex and high-precision containers at its GMP fill-finish facility.

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ABOUT THE AUTHORS

Andrea Allmendinger, PhD, has been Chief Scientific Officer at ten23 health since November 2021. Dr Allmendinger is also Adjunct Professor and Group Leader at the University of Freiburg (Baden-Württemberg, Germany), researching novel parenteral drug formulations and device solutions to improve stability, usability and cost of goods. Between 2010 and 2021, she was Principal Scientist, Pharmaceutical Development at Roche, working on inter alia manufacturability and injectability of high-concentration formulations, syringe and high-volume drug/device combination products, particulates and surfactant strategy. Dr Allmendinger studied Pharmacy at the University of Heidelberg (Germany) and University College London (UK), and holds a PhD in Pharmaceutical Sciences from the University of Basel, Switzerland. She obtained the *venia legendi* (German Habilitation) from the University of Freiburg in 2021, and serves as Editor-In-Chief for the AAPS Open Journal.

Professor Hanns-Christian Mahler, PhD, is Chief Enablement Officer and a Board Member at ten23 health. He previously led the Drug Product Services Business Unit at Lonza AG (Basel, Switzerland) (2015–2021) and worked in various leadership roles, such as Head of Pharmaceutical Development & Supplies at Roche (2005–2015) and Merck KGaA (2000–2005). He has extensive expertise in formulation development, process development and validation, packaging/device development and integration, sterile manufacturing and regulatory submissions with numerous IND/IMPD and BLAs. Professor Mahler studied pharmacy at the University of Mainz (Germany), and holds a PhD in toxicology from the Institute of Pharmacy, University of Mainz, and pharmacist specialisation degrees in toxicology and ecology, and pharmaceutical technology. He also has qualifications in Business and Marketing (AKAD University, Germany). Professor Mahler obtained his *venia legendi* from the University of Frankfurt (Germany) in 2010 and is adjunct faculty member and lecturer at the universities of Frankfurt and Basel. He also serves as Editor for Pharmaceutical Research, Journal of Pharmaceutical Sciences, AAPS Open Journal and PDA Journal of Pharmaceutical Sciences and Technology.

Dr Philipp Behrendt has been a Quality Assurance Manager at ten23 health since February 2023 and is an accomplished professional with a broad background in the pharmaceutical and biotechnology industries, showcasing an in-depth knowledge in quality assurance, validation, project management and leadership. His previous positions were at Lonza, Novartis and Aenova. He holds a PhD in physical chemistry from the University of Marburg (Germany).

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