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

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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]

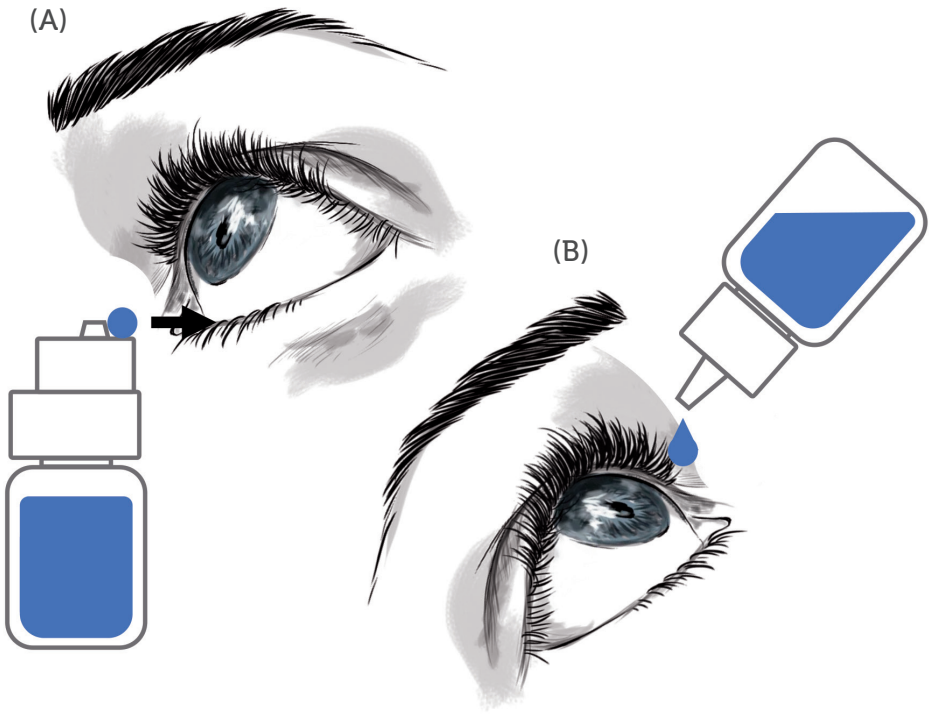

Figure 1: The application vs instillation of eye drop medication. A) Application: the patient keeps their head straight, and upon opening of the conjunctival fold, the eye drop is transferred to the eye with the new MD eye bottle in an upright position. B) Instillation: the patient reclines their head 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?

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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.

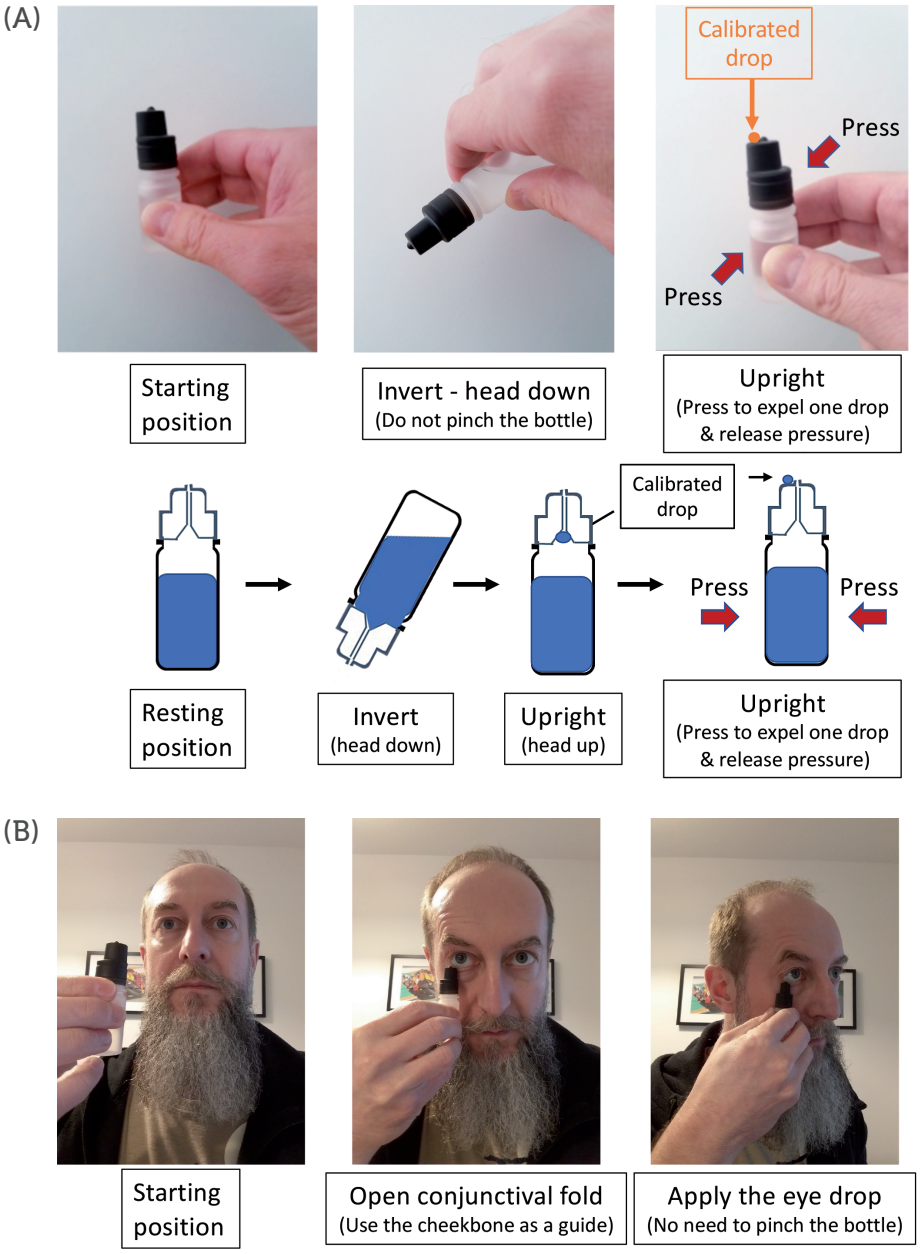

Figure 2: Schematic representation of the two-step application procedure of the new MD eye bottle. (A) actuation and (B) application steps of a single, well-calibrated eye drop with the new MD eye bottle.

> "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,

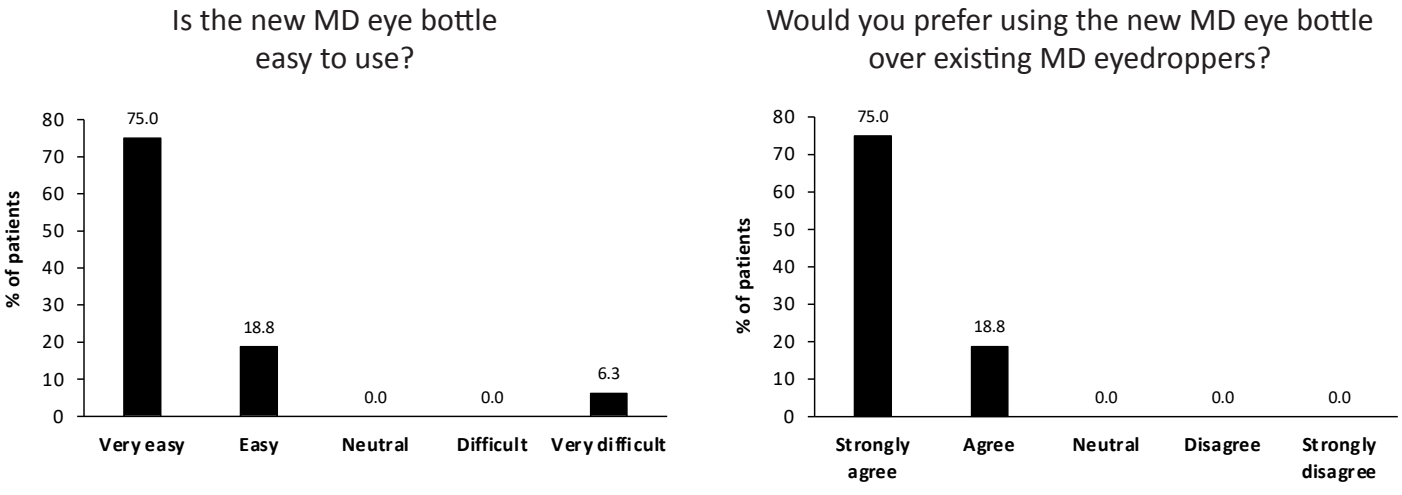

Figure 3. Usability testing results for new MD eye bottle.

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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