FDA Executive Summary

Prepared for the November 10, 2022 Meeting of the Ophthalmic Devices Panel

Classification of Ophthalmic Dispensers

Product Code: LXQ

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1. Introduction

Per Section 513(b) of the Food, Drug, and Cosmetic Act (the Act), the Food and Drug Administration (FDA) is convening the Ophthalmic Devices Advisory Panel (the Panel) for the purpose of obtaining recommendations regarding the classification of ophthalmic dispensers, a pre-amendments device type which remains unclassified. Specifically, the FDA will ask the Panel to provide recommendations regarding the regulatory classification of ophthalmic dispensers under product code "LXQ." The device names and associated product codes are developed by the Center for Devices and Radiological Health (CDRH) in order to identify the generic category of a device for FDA. While most of these product codes are associated with a device classification regulation, some product codes, including "LXQ," remain unclassified.

FDA is holding this panel meeting to obtain input on the risks to health and benefits of ophthalmic dispensers under product code "LXQ." The Panel will discuss whether ophthalmic dispensers under product code "LXQ" should be classified into Class I (subject only to General Controls).

1.1 Current Regulatory Pathways

Ophthalmic dispensers, including eye cups and droppers, are a pre-amendment, unclassified device type. This means that this device type was marketed prior to the Medical Device Amendments of 1976 but was not classified by the original classification panels. Currently, ophthalmic dispensers are being regulated through the 510(k) pathway, and are cleared for marketing if their intended use and technological characteristics are "substantially equivalent" to a legally marketed predicate device. Since these devices are unclassified, there is no regulation associated with the product code.

1.2 Device Description

Ophthalmic dispensers are intended to deliver ophthalmic liquids to the eye, either to irrigate or to deliver medication. There are different types of ophthalmic dispensers, some of which are discussed below.

Eye cups are cup-shaped devices used to temporarily hold liquids such as saline, eye wash solution, or other medication. An eye cup is fitted and inverted over the eye to allow the solution to irrigate, wash out, or flush the affected eye.

Droppers are intended to instill ophthalmic medication dropwise into the eye. They may have a squeezable pipette bulb. They may consist of the pipette and bulb only or may be designed as a closure for a storage container or are squeezable bottles with a tapered tip and cap.

2. Regulatory History

The Advance Diagnostics Disposable Eyecup manufactured by Advantage Diagnostics Corp was the first device under product code "LXQ" to be cleared by FDA on May 13, 1988. The FDA determined that the Advance Diagnostics Disposable Eyecup was substantially equivalent to pre-amendment eye cup devices. Table 1 below shows the manufacturers, device names, and associated 510(k) submission numbers for FDA-cleared ophthalmic dispensers.

Table 1: 510(k) Clearances for Ophthalmic Dispensers

510(k) Number	Trade Name	Sponsor
K881369	Advance Diagnostics Disposable Eyecup	ADVANTAGE DIAGNOSTICS CORP
K971134	Vista Eyeshower	JOHN BRANCH
K051414	Eye Cup, Sterile 1 and Non Sterile	TOLLOT PTY.LTD. (AAXIS PACIFIC)
K140409	Flents Plastic Eye Wash Cup	APOTHECARY PRODUCTS, INC.
K151575	Dynarex Eye Cups	DYNAREX CORPORATION

3. Indications for Use

The Indications for Use (IFU) statement identifies the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended. Representative Indications for Use statements for ophthalmic dispensers include the following:

- Intended to hold and place liquids such as eye wash solutions, over the eye to allow the solution to wash out or flush the affected eye.
- Intended for instilling ophthalmic medication dropwise to the eye.

4. Clinical Background

4.1 Clinical Use

There is a wide variety of ocular symptoms and conditions that are treated with liquids, including ophthalmic solutions, gels, suspensions, and emulsions. Administration via a liquid maximizes the concentration of the liquid in the anterior segment of the eye while minimizing the introduction of the liquid into the rest of the body. Liquids intended for this purpose are administered dropwise due to the extremely limited volume capacity of the ocular surface, particularly the tear film (approximately 3 microliters). Liquids not administered dropwise, but instead

administered ad hoc in large volumes well exceeding the volume capacity of the tear film, are used to flush debris or foreign material off the ocular surface, whose presence may cause ocular pain or discomfort. Obtaining a patient's clinical history and/or performing clinical examination of the eye will help determine the need to use a liquid, the kind of liquid to use, and how to administer it.

4.2 Risks

FDA has identified the following risks to health associated with ophthalmic dispensers:

Table 2: Risks to Health and Descriptions/Examples for Ophthalmic Dispensers

Identified Risk	Description/Examples
Infection	• This can result from a new device that has microbial contamination as packaged or a device that becomes microbially contaminated because it is improperly cleaned and re-used. • This can result from the microbial contamination of the ophthalmic dispenser and ophthalmic medication because the dispenser tip has touched the eye or touched another unintended surface.
Adverse tissue reaction	• This can result from the use of device materials that are not biocompatible. • This can result from the interaction between the device and ophthalmic medication (for example, chemicals from the device leach into the ophthalmic medication).
Compromised treatment	• This can result from a damaged or defective device. • This can result from inadequate instructions and the device not being used as intended. • Design of dispenser may cause incorrect dosage of medication to be dispensed to the patient.
Mechanical Injury	• This can result from unintended direct physical contact of the eye with the device.

The Panel will be asked whether this list is a complete and accurate list of the risks to health presented by ophthalmic dispensers under product code "LXQ", and whether any other risks should be included in the overall risk assessment of this device type.

5. Literature Review

5.1 Methods

A systematic literature review was conducted to gather any published information regarding the safety of ophthalmic dispensers.

Online literature searches were performed in two electronic databases (Embase and PubMed) using variations of the terms "eye cup," "droptainer," and "eyedropper" as well as limits placed by study design and date. The search was limited to human clinical studies published in the English language, with publication dates between January 1, 1976, and May 11, 2022. Database filters were used to exclude non-clinical studies, case reports on nine people or fewer, economic and cost-effectiveness analyses, narrative reviews, conference abstracts/proceedings, commentaries, and editorials.

For the search terms used for the literature search, please see Appendix A. Additional inclusion, exclusion, and cross-refencing of literature was done to identify relevant publications. The flow diagram in Appendix B represents the total number of articles obtained.

5.2 Results

The initial search yielded 270 articles. After duplicate articles between databases were removed, 185 articles remained. Following a review of the titles and abstracts, 13 articles remained for full-text review. Of these, five articles were determined to be relevant to the safety of ophthalmic dispensers. The number and reason for each excluded article is also summarized in the flow diagram in Appendix B.

The five articles consist of the following: three prospective, randomized trials (Brand et al. 2021; Sakiyalak et al. 2014; Averns et al. 1999); one prospective, comparative trial (Gomes et al. 2016); one repeated-measures case series (Sanchez et al. 2021).

To supplement the original literature yield, 10 additional relevant articles were identified by cross-referencing citations found in the above articles. These consist of the following: a prospective case series (Solomon et al. 2003); two prospective case-control studies (Geyer et al. 1995; Schein et al. 1992); two prospective, observational studies (Teuchner et al. 2015; Jokl et al., 2007); three case series of fewer than nine patients (Schein et al. 1988; Templeton et al. 1982; Alfonso et al. 1987); two laboratory studies (Coad et al. 1984; Høvding et al. 1982).

A total of 15 relevant articles were identified through this process. Please see Appendix C for the reference list (bibliography) for the 15 articles identified as relevant. Articles that were erroneously excluded from the original yield and articles identified by cross-referencing are identified.

5.3 Adverse Events Associated with Ophthalmic Dispensers

Three articles reported bacterial infection of the eye (keratitis or corneoscleritis) associated with bacterial contamination of the ophthalmic dispenser used by the affected patients. Templeton et al. described three patients who developed *Serratia marcescens* keratitis after penetrating keratoplasty. Despite intensive treatment, the transplanted corneal graft failed in one patient and resultant corneal scarring in the visual axis necessitated a second keratoplasty in another. *S. marcescens* was isolated from the outer grooves of the dispensers being used by the patients (containing topical prednisolone sodium phosphate in two, timolol 0.5% ophthalmic solution in one) and from the inner surfaces of the dispenser caps. It was suspected that moisture collecting in the dead space between the cap and bottle could have been a culture medium for the bacteria. Schein et al. 1987 described seven cases of severe keratitis due to gram-negative bacteria associated with the use of contaminated topical ocular medications and contaminated ophthalmic dispensers. In each case the same bacteria cultured from corneal scrapings were also isolated from the medication (timolol or prednisolone actetate) in the dispenser, and in two cases, the same bacteria was also isolated from the dispenser. One patient required enucleation of the infected eye. One required a penetrating keratoplasty and intraocular lens exchange. Dense corneal scarring developed in four patients, one of whom also required retrobulbar alcohol injections for intractable ocular pain. In three of the seven cases, there was a history of prior minor trauma or disruption of the corneal epithelium (abrasion with a mascara brush, applanation, and suture removal).

Alfonso et al. describe three cases of *Pseudomonas aeruginosa* corneoscleritis of which one was associated with the use of timolol ophthalmic solution contained in an ophthalmic dispenser with a contaminated bottle cap interior. In this case, there had been prior minor ocular trauma with a mascara brush before the onset of symptoms. This patient developed a severe infection requiring hospitalization for intravenous antibiotics and eventually developed severe ocular pain requiring retrobulbar alcohol injection.

Solomon et al. reported on a series of 12 patients with acute conjunctival inflammation caused by non-intentional contact of ophthalmic dispensers with the conjunctiva during the self-administration of topical ophthalmic solutions or ointments. These 12 patients had at baseline corneal conditions such as herpetic keratitis, or status post ocular surgery (cataract extraction; penetrating keratoplasty; laser in-situ keratomileusis). They presented with sudden onset of a painful, red eye and were observed to have corneal epithelial erosion in the lower bulbar conjunctiva with surrounding hyperemia and conjunctival edema. This was determined to be self-induced injury from inappropriate use of the ophthalmic dispenser. Notably, none of the patients had been aware of the possibility that their injuries were self-induced.

Recognizing that microbial contamination of ophthalmic dispensers has potential safety implications regarding infection risk, several studies examined the potential for droptainers to be contaminated by inappropriate contact to the ocular surface or

periocular area and the frequency of contamination in healthy adult populations and certain patient populations who regularly use ophthalmic solutions.

Five studies evaluating the use of eyedrop guides in conjunction with droptainers reported contamination of the tip through contact with the eye. In a prospective, cross-sectional, randomized trial of 26 participants, Brand et al. reported inadvertent bottle tip touch in 46% without the use of an eyedrop guide. In a prospective, cross-sectional, comparative trial of 23 participants, Gomes et al. reported inadvertent bottle tip touch to the globe or periocular tissues in 35% of the cohort when no eyedrop guide was used. In a repeated-measures case series of 50 participants, Sanchez et al. reported bottle tip touch in 33% of investigated eyes when no eyedrop guide or prior teaching was utilized. In a prospective, randomized, crossover study of 59 glaucoma patients trained to use an eyedrop guide, Sakiyalak et al. reported that 11.9% of the participants still inadvertently contaminated liquid by dispensing into the guide before dispensing into the eye; 22% contaminated the bottle tips with the eyes or periocular tissues when instilling with the traditional technique. In a prospective, randomized crossover study of 29 participants with rheumatoid arthritis and dry eye syndrome, Averns et al. found that 76% touched their eye or conjunctiva with the bottle tip versus none with the eyedrop guide.

Six studies evaluated microbial contamination of ophthalmic dispensers either by culturing droptainers used by patients (Teuchner et al., 2015; Jokl et al., 2007; Geyer et al. 1995; Schein et al. 1992; Høvding et al. 1982) or by direct inoculation of eyedroppers (Coad et al. 1984). A sampling of over 400 droptainers collected over 11 months from various clinical and home settings demonstrated bacterial contamination of 24.4% of the bottles, the majority (62%) of which involved contamination of the tip only. 21% of the contaminated home samples were comprised of known human pathogens such as *Pseudomonas aeruginosa* (Teuchner et al. 2015). Jokl et al. 2007 collected and cultured 123 droptainers from 47 patients in a long-term care facility and found bacterial contamination in 8% of the bottles. Geyer et al. similarly collected and cultured 194 droptainers and also cultured the conjunctiva from 109 glaucoma patients. They found that 28% of bottles were contaminated, 20% tip vs. 8% liquid only. There was a correlation between length of time of bottle use and contamination likelihood; bottles in use for ≤8 weeks had a 19-20% contamination rate while those in use for >9 weeks had a 40-41% contamination rate, a difference that was statistically significant. Based on these findings, Geyer et al. recommended regular replacement of opened bottles and proper precautions and directions for using the medication inside the bottle to minimize the risk of microbial contamination.

In a prospective, case-control study, Schein et al. 1992 collected 220 ophthalmic medications from 101 participants with non-microbial ocular surface disease and cultured the bottle caps and interior contents as well as the conjunctiva of the participants: 42% of participants had at least one medication contaminated at one or more sites and 29% of bottles had contamination from at least one site. The bottle cap had the highest proportion of contamination compared to the other sites. The

authors suggest that the bottle cap serves as a reservoir of contamination that may lead to subsequent colonization of the contents of the bottle. Høvding et al. 1982 conducted a laboratory study in which 638 multi-dose droptainers already in use by patients were collected over a range of time. 72 of these were eyedropper bottles or "pipette bottles." Cultures were performed from directly dispensed drops and swabs of the dropper tips. 38 of 180 (21.1%) dropper tips yielded bacterial growth. None of the pipette aspirates yielded microorganisms. The authors conclude that bottle dropper tips may be frequently contaminated and "care should be taken to ensure aseptical administering of the eye drops. This is particularly important if the same bottle is used at short intervals to different patients." Coad et al. 1984 conducted a laboratory study in which the tips of eyedropper pipettes and of droptainers ("squeeze bottles") containing Fluress® were inoculated with *Pseudomonas aeruginosa*. Drops from the bottles and swabs from inside of the caps were then cultured. The authors found no growth from the swabbings of the caps of the eyedropper bottles but the swabbings from the caps of the "squeeze bottles consistently yielded bacteria for 24 hours."

5.4 Overall Literature Review Conclusions

There is very little available literature specifically on ophthalmic dispensers. The majority of the relevant literature found only pertained to droptainers and only one article specifically included eyedroppers or "pipette"-type bottles. Several studies of eye dropper guides and several studies evaluating the culture results of collected bottles demonstrate that it is common for patients to inadvertently contaminate the dispenser and for bottles to become contaminated with extended, repeated use. A few very small case series and case reports show the risk for potentially serious adverse events of infection due to microbial contamination of ophthalmic dispensers, particularly those used on a regular basis by patients, as well as the potential for ocular injury due to inadvertent trauma by the dispenser. While infection secondary to contamination may have the potential to become serious, it does not appear that secondary infection is a common occurrence, as these case reports have very small sample sizes and were published from >30 years ago, with no similar cases identified since. However, there are no large clinical studies prospectively examining the rate of infection secondary to dispenser contamination. The other potential adverse event reported is sequelae of inadvertent trauma to the eye with the dispenser. Since this was reported in only one study, the true prevalence of these adverse events remains unclear but may be assumed to also be low. Therefore, it may be concluded that ophthalmic dispensers such as droptainers and eyedroppers are generally low in risk. Given there was no relevant literature found for eye cups, it may be reasonable to assume that eye cups would likely present even lower risk than droptainers and eyedroppers.

6. Risks to Health Identified through Medical Device Reports (MDRs)

6.1 Overview of the MDR System

The MDR system provides FDA with information on medical device performance from patients, health care professionals, consumers and mandatory reporters (manufacturers, importers and device user facilities). The FDA receives MDRs of suspected device-associated deaths, serious injuries, and certain malfunctions. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDRs can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting/environment

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the submission of incomplete, inaccurate, untimely, unverified, duplicated or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about the frequency of device use. Finally, the existence of an adverse event report does not definitively establish a causal link between the device and the reported event. Because of these limitations, MDRs comprise only one of the FDA's tools for assessing device performance. As such, MDR numbers and data should be taken in the context of the other available scientific information.

6.2 MDR Data: Ophthalmic Dispensers

The Agency searched the medical device reports databases to identify adverse events related to ophthalmic dispensers. In order to capture as many potentially relevant MDRs as possible, the search terms were broad and included the product code LXQ, the 510(k) clearance numbers listed in Table 1, and a number of general terms for different types of ophthalmic dispensers or related to ophthalmic dispensers including: eye cup, eyecup, eye dropper, eyedropper, eye drop, eyedrop, droptainer, eye dispenser, ophthalmic dispenser, ophthalmic, dropper, and other similar terms. The search was performed with no start date and an ending date of August 15, 2022.

Initially, given the broad and general search terms used, 1,741 potentially relevant MDRs were identified. After review of these reports, there were 67 reports that were found to be duplicates of others and therefore these duplicates were removed from the overall count. The remaining 1,674 MDRs were reviewed for the manufacturer name, brand name, generic name, product code, premarket submission number if provided and/or applicable, and narrative report. Based on this information, MDRs that were not relevant to the scope of the panel were excluded. Examples of reasons for exclusion were MDRs reported for ophthalmic device types that are not ophthalmic dispensers and, therefore, outside the scope of this panel. Other reasons

for exclusion included that the device described was clearly not an ophthalmic device and, therefore, also was not relevant to this panel.

After completion of this individual MDR review process, three MDRs were identified as being relevant to ophthalmic dispensers. These three MDRs were all related to difficulties experienced by patients using different ophthalmic dispensers to self-administer ophthalmic medication. Brief summaries of these three MDRs are below, with more detailed information about each in Appendix D.

One MDR, submitted and received February 17, 2015, was a voluntary report from a patient using "glaucoma and tissue rejection drugs" who expressed a general concern that "plastic squeeze dropper bottles" used for these ophthalmic drugs posed risks to patients if they are "opaque" and he could not see whether he needed to obtain replacement supply before the bottle is empty. The patient stated that this "is an issue involving the entire pharmaceutical industry that uses plastic squeeze dropper bottles." Although not specifically stated, this MDR appears to be about droptainers, one type of ophthalmic dispenser.

One MDR submitted, received on March 9, 2021, refers to a patient reported concern that there were "sharp plastic corners on either side of the dropper, which makes it very hard to maneuver" and she "feels the dropper is hard to use."

One MDR was submitted on July 11, 2022, and received July 22, 2022. This MDR was a voluntary report from a pharmacist on behalf of a patient who was prescribed a biologic for neurotrophic keratoconjunctivitis of the right eye. The publicly available labeling of this biologic product indicates that this is a self-administered medication that comes in a specially designed vial and ophthalmic dispenser. The dispenser is a "pipette" with a plunger that is designed to connect to the vial top, uptake the medication from the inverted vial, detach from the vial top, and deliver the eye drop to the eye when the plunger is pressed. The patient complaint was that when he pushes the plunger, "the medicine squirts out" and that "it's very difficult to control how much medicine gets into the eye."

7. Recall History

7.1 Overview of Recall Database

The Medical Device Recall database contains Medical Device Recalls classified since November 2002. Since January 2017, it may also include correction or removal actions initiated by a firm prior to review by the FDA. The status is updated if the FDA identifies a violation and classifies the action as a recall and again when the recall is terminated. FDA recall classification may occur after the firm recalling the medical device product conducts and communicates with its customers about the recall. Therefore, the recall information posting date ("create date") identified on the database indicates the date FDA classified the recall, it does not necessarily mean that the recall is new.

7.2 Recall Results: Ophthalmic Dispensers

The Agency performed a search of the Medical Device Recall database to identify any recalls related to ophthalmic dispensers. There was no starting date, and the end date of this search was August 15, 2022. General search terms were used, such as eye cup, eyecup, eye dropper, eyedropper, eye drop, eyedrop, droptainer, eye dispenser, ophthalmic dispenser, ophthalmic, and other similar terms. The search did not identify any relevant recalls regarding ophthalmic dispensers, including eye cups, eye droppers, or droptainers. Thus, there were no relevant recalls classified by CDRH.

8. Summary

In light of the information available, the Panel will be asked to comment on whether ophthalmic dispensers under product code "LXQ":

meet the statutory definition of a Class III device in accordance with section 513 of the Food, Drug, and Cosmetic Act (FD&C Act):

- insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and

- the device is purported or represented to be for a use in supporting or sustaining human life, or for a use which is of substantial importance in preventing impairment of human health, or

- if the device presents a potential unreasonable risk of illness or injury

or would be more appropriately regulated as Class II, in which:

- general and special controls, which may include performance standards, postmarket surveillance, patient registries and/or development of guidelines, are sufficient to provide reasonable assurance of safety and effectiveness;

or as Class I, in which:

- the device is subject only to general controls, which include registration and listing, good manufacturing practices (GMPs), prohibition against adulteration and misbranding, and labeling devices according to FDA regulations.

For the purposes of classification, FDA also considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. The persons for whose use the device is represented or intended;

2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;

3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and

4. The reliability of the device.

The Panel will be asked whether they believe ophthalmic dispensers would be appropriately regulated as Class I. If the Panel does not agree with FDA's proposed classification, the Panel will be asked to provide their rationale for recommending a different classification.

8.1 Special Controls

For ophthalmic dispensers intended to irrigate the eye or provide controlled instillation of ophthalmic medication dropwise to the eye, FDA does not believe that special controls will be required and that general controls will be sufficient to provide a reasonable assurance of the safety and effectiveness of ophthalmic dispensers.

8.2 Overview of Proposed Classification/FDA Recommendation

Based on the safety and effectiveness information gathered by the FDA, the identified risks to health and recommended mitigation measures, we recommend that ophthalmic dispensers indicated for use to irrigate the eye or provide controlled instillation of ophthalmic medication dropwise to the eye be regulated as Class I [exempt] devices.

886.5880 Ophthalmic Dispensers.

(a) *Identification.*

Ophthalmic dispensers are manual devices that are intended to irrigate the eye or provide controlled instillation of ophthalmic medication.

(b) *Classification.*

Class I (general controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter, subject to the limitations in § 886.9.

Based on the available scientific evidence, the FDA will ask the Panel for their recommendation on the appropriate classification of the ophthalmic dispensers under product code "LXQ."

Appendix A: Literature Search Terms for Ophthalmic Dispensers

Table 3: Literature Search Terms: PubMed (May 23, 2022)

Search number	Query	Results
Filters: Humans, English, from 1976/1/1 - 2022/5/11		
#3	#1 NOT #2	**139**
#2	comment[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR "Book Illustrations"[pt] OR congress[pt] annual[tiab] OR book[tiab] OR "conference poster"[tiab] OR "conference abstract"[tiab] OR "conference paper"[tiab] OR "conference proceeding"[tiab] OR "conference review"[tiab] OR congress[tiab] OR editorial[tiab] OR erratum[tiab] OR letter[tiab] OR note[tiab] OR meeting[tiab] OR sessions[tiab] OR "short survey"[tiab] OR symposium[tiab]	318,682
#1	"eye drop delivery"[tiab] OR "eye cup"[tiab] OR eyecup[tiab] OR "eye dropper"[tiab] OR eyedropper[tiab] OR "eye drop dispenser"[tiab] OR droptainer[tiab] OR "eye drop guide"[tiab] OR "eye cups"[tiab] OR eyecups[tiab] OR "eye droppers"[tiab] OR eyedroppers[tiab] OR "eye drop dispensers"[tiab] OR droptainers[tiab]	139

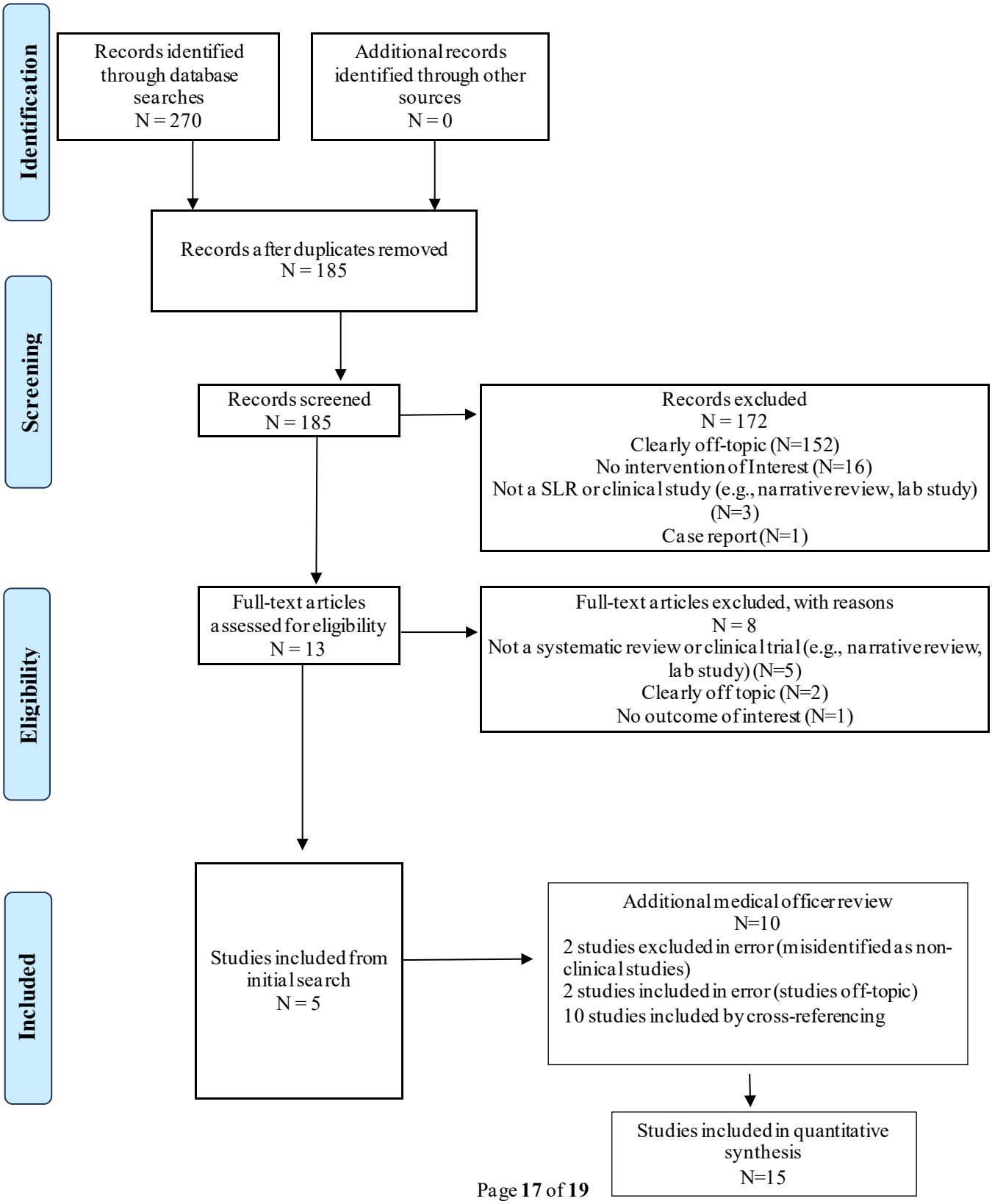
Table 4: Literature Search Terms: Embase (May 23, 2022)

Search number	Query	Results
Filters: Humans, English, from 1976 - 2022		
#3	#1 NOT #2	**131**
#2	(('editorial'/exp OR 'letter'/exp OR 'medical illustration'/exp OR 'book'/exp OR 'poster'/exp OR 'conference abstract'/exp OR 'conference paper'/exp OR 'conferences and congresses'/exp OR 'conference review'/exp OR 'erratum'/exp OR 'symposium'/exp OR 'short survey'/exp OR 'note'/exp) AND 'article in press'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it OR abstract:nc OR annual:nc OR conference:nc OR 'conference abstract':it OR 'conference paper':it OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR editorial:it OR letter:it OR note:it OR meeting:nc OR sessions:nc OR symposium:nc OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim OR comment:ti OR book:pt OR comment:ab,ti OR annual:ab,ti OR 'conference proceeding':ab,ti OR note:ab,ti OR meeting:ab,ti OR sessions:ab,ti OR 'short survey':ab,ti) AND [1976-2022]/py AND [english]/lim AND [humans]/lim	8,348,576

#1	('eye drop delivery aid'/exp OR 'eye drop delivery aid':ab,ti OR 'eye cup':ab,ti OR eyecup:ab,ti OR 'eye dropper':ab,ti OR eyedropper:ab,ti OR 'eye drop dispenser':ab,ti OR droptainer:ab,ti OR 'eye drop guide*':ab,ti OR 'eye cups':ab,ti OR eyecups:ab,ti OR 'eye droppers':ab,ti OR eyedroppers:ab,ti OR 'eye drop dispensers':ab,ti OR droptainers:ab,ti) AND [english]/lim AND [humans]/lim AND [1976-2022]/py	208

Appendix B: Literature Search PRISMA

Figure 1: Literature Search PRISMA



Appendix C: Literature Search References

1. *Alfonso, E.; Kenyon, K.R.; Ormerod, L.D.; Stevens, R.; Wagoner, M.D.; Albert, D.M. Pseudomonas corneoscleritis. Am. J. Ophthalmol. 1987, 103, 90–98.
2. Averns H, Hall J, Webley M. Role of opticare eye drop delivery system in patients with rheumatoid arthritis. J Rheumatol. Dec 1999;26(12):2615-8.
3. †Brand G, Hecht I, Burgansky-Eliash Z, et al. Comparison of the usability of eye drop aids and the conventional bottle. Article. Journal of Clinical Medicine. 2021;10(23)doi:10.3390/jcm10235658
4. *Coad, C. T., Osato, M. S., and Wilhelmus, K. R. Bacterial contamination of eyedrop dispensers. Am. J. Ophthalmol. 98:548, 1984.
5. *Geyer O, Bottone EJ, Podos SM, et al. Microbial contamination of medications used to treat glaucoma. Br J Ophthalmol. 1995;79(4):376e9.
6. †Gomes BF, Lordello M, Celli LF, Santhiago MR, Moraes HV. Comparison of eyedrop instillation technique with and without a delivery device in inexperienced patients. Eur J Ophthalmol. 2016;26(6):594-597. doi:10.5301/ejo.5000797.
7. *Høvding, G., and Sjursen, H.: Bacterial contamination of drops and dropper tips of in-use multidose eye drop bottles. Acta Ophthalmol. 60:213, 1982.
8. *Jokl, D.H.K.; Wormser, G.P.; Nichols, N.S.; Montecalvo, M.A.; Karmen, C.L. Bacterial contamination of ophthalmic solutions used in an extended care facility. Br. J. Ophthalmol. 2007, 91, 1308–1310.
9. Sakiyalak D, Maneephagaphun K, Metheetrairat A, Ruangvaravate N, Kitnarong N. The effect of the Thai "Eye Drop Guide" on success rate of eye drop self-instillation by glaucoma patients. Asian Biomedicine. 2014;8(2):221-227. doi:10.5372/1905-7415.0802.282
10. Sanchez FG, Mansberger SL, Kung Y, et al. Novel Eye Drop Delivery Aid Improves Outcomes and Satisfaction. Article. Ophthalmology Glaucoma. 2021;4(5):440-446. doi:10.1016/j.ogla.2021.01.001
11. *Schein OD, Wasson PJ, Boruchoff SA, et al. Microbial keratitis associated with contaminated ocular medications. Am J Ophthalmol. 1988;105:361–365.
12. *Schein OD, Hibberd PL, Starck T, et al. Microbial contamination of in-use ocular medications. Arch Ophthalmol. 1992;110(1):82e5.
13. *Solomon, A.; Chowers, I.; Raiskup, F.; Siganos, C.S.; Frucht-Pery, J. Inadvertent conjunctival trauma related to contact with drug container tips: A Masquerade syndrome. Ophthalmology 2003, 110, 796–800.
14. *Templeton, W.C.; Eiferman, R.A.; Snyder, J.W.; Melo, J.C.; Raff, M.J. Serratia keratitis transmitted by contaminated eyedroppers. Am. J. Ophthalmol. 1982, 93, 723–726.
15. *Teuchner B, Wagner J, Bechrakis NE, et al. Microbial contamination of glaucoma eyedrops used by patients compared with ocular medications used in the hospital. Medicine (Baltimore). 2015;94(8):e583

*Identified via cross-referencing.
†Erroneously excluded from original yield.

Appendix D: Medical Device Report (MDR) Information on Ophthalmic Dispensers

Table 5: MDR Information on Ophthalmic Dispensers from MAUDE Database

Reporter Country Code	Type of Report	Report Date / Date FDA received	Device Problem (Summary Code)	Device Reported in MDR	Narrative Report
United States	Voluntary report from patient	Report Date: February 17, 2015 Date FDA Received: February 17, 2015	"Adverse Event Without Identified Device or Use Problem"	"Opaque Plastic Sq[u]eeze Dropper Bottle"	"This is an issue involving the entire pharmaceutical industry that uses plastic squeeze dropper bottles. These are what contain the ophthalmic drugs that have been prescribed for me. The containers are opaque, and the pt cannot tell whether he is almost out of medicine. It would be most beneficial to be able to see that only a few days worth of the drug is left, so that a replacement supply can be obtained before the bottle is empty. Some patients get pharmaceuticals through the mail, so that needs to be considered. This is a serious matter. Diagnosis or reason for use: glaucoma and tissue rejection drug containers.
United States	Voluntary report from patient	Report Date: March 9, 2021 Date FDA Received: March 9, 2021	"Scratched Material"	"Dropper"	"Patient stated that the eye dropper has sharp plastic corners on either side of the dropper, which makes it very hard to maneuver. She stated she loves the medication and has had no adverse event, but she feels the dropper is hard to use."
United States	Voluntary report from pharmacist	Report Date: July 11, 2022 Date FDA Received: July 22, 2022	"Fluid Leak" "Use of Device Problem"	"Pipette"	"Pt will contact dompe to complain about the pipettes being difficult to use. He states that when he pushes the plunger. The medicine squirts out. "He says it is difficult to control how much medicine gets in the eye." "Diagnosis for use: neurotrophic keratoconjunctivitis of right eye."