

Preservative-Free Ophthalmic Products

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1. Preservative-free Ophthalmic Products – The Need

Over the years, preserved topical medications have remained the basis of treatment for various ocular diseases, such as glaucoma, dry eye syndrome, infections, uveitic diseases, and ocular hypertension. To treat eye-related disorders, patients are often prescribed to use different medications under treatment regimens of varying length. In most of the ophthalmic medicaments, preservatives are added, as mandated, to prevent the growth of microbial contaminants and biodegradation. Thus, preservatives have become a key component in ophthalmic solutions such as prostaglandin analogues, first-line drugs used in the management of glaucoma, IOP-lowering drugs, artificial tears and antibiotics.

Though preservatives help keep the containers sterile over the course of multiple uses, they cause ocular irritation and allergies in certain individuals. Owing to the potential adverse effects of ophthalmic preservatives, there is an increasing need for preservative-free ophthalmic products among the consumers. Given the scenario, there has been a surge in the pharmaceutical industry to develop preservative-free medications.

However, preservative-free ophthalmic products in multi-dose delivery are at a high risk of contamination, which can be addressed best by microbial contamination-resistant containers. Thus, the demand for innovations and improvements in the packing/dispensing technology has also been increasing.

2. The Industry Thriving

Ophthalmic is an expanding market driven by increasing prevalence of eye disorders particularly among the elderly population, such as age-related macular degeneration (AMD), diabetic retinopathy (DR), and presbyopia. In addition, a huge segment of population across the globe experiences various surface eye diseases, such as dry eye syndrome, glaucoma, conjunctivitis, cataract, diabetic retinopathy, red eye, macular degeneration, uveitis etc, and the number is expected to grow further by 2020. As a result, recent market researches has revealed that during 2012 to 2022, the pharmaceutical industry will focus on improving treatment of ocular disorders, laying strong emphasis on R&D for treating eye diseases.

A wide range ophthalmic medication to treat various eye diseases via different processes has evolved in the market. Based on the applications, ophthalmology drugs are classified as:

- Treatment based drugs - provided based on the diagnosed conditions; classified as dry eye drugs, retinal disorder drugs, anti-allergy/inflammatory/infective drugs and anti-glaucoma drugs
- Over the counter drugs (OTC) - procured without any need of a prescription
- Ocular anesthetics - administered by surgeons during surgery

As the demand grows, there are high unmet clinical needs and huge commercial opportunities in the market, especially to develop ophthalmic products with nil or minimal side effects.

3. Preservatives and the effects

In ophthalmic preparations, preservatives are a key component to curb microbial activity; they also help prevent contamination, decomposition of active drugs and keep them stable. Various preservatives are being used in ophthalmic preparations; common among them are:

- Benzalkonium chloride (BAC/BAK)
- Benzododecinium bromide (BDB)
- Stabilized Oxychloro Complex (Purite)
- SofZia
- Polyquaternium-1 (PQ-1) ((Polyquad)
- Cetrimide (Cetrimonium)
- Chlorhexidine
- Chlorobutanol
- Disodium edetate (EDTA)
- Methylparahydroxybenzoate
- Phenylmercuric nitrate
- Polyhexamethylene biguanide hydrochloride (PHMB)
- Sodium perborate (GenAqua)
- Sorbic acid
- Thimerosal
- Polixetonium (Polyquaternium-42)

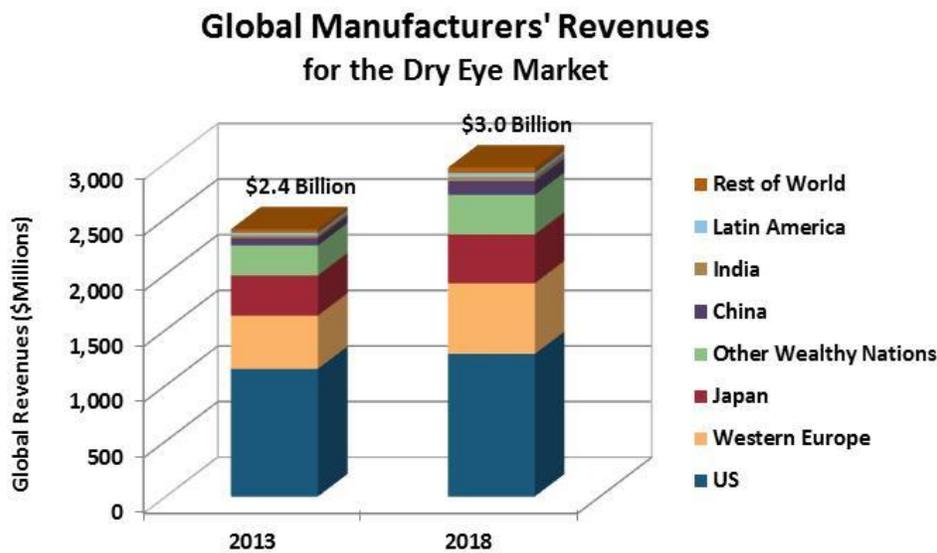
Unlike most medications of other specialties, many ophthalmic products with preservatives are topical. But, exposure to preservatives is a major reason for the development of adverse effects as they have a potential to cause toxicity to the ocular surface, especially in the long-term therapies. Continuous exposure to these preservatives can result in various side effects, such as dryness, irritation, burning sensation, itching, corneal damage, cellular damage to the conjunctiva, chronic allergic blepharitis, surface epithelial cell loss etc.

Despite the evidence of adverse side effects, majority of patients throughout the world are prescribed to administer preserved eye-drops.

4. The Market - Overview

Ophthalmic products are a niche segment in the healthcare industry; they include prescription medicine for treatments, products used during and post eye surgery, diagnostic devices, surgical systems, intraocular lens (IOL) implants and disposables, in-office products for eye care professionals and over-the-counter (OTC) products. The \$16.2bn ophthalmic pharmaceutical market does significant contributions to the growth of the healthcare market.

There are an increasing number of eye disorders and visual impairments, especially in developing countries, due to aging population. In addition, diseases such as diabetes too are cause of visual disorders. Various international organizations are channelizing their efforts to increase the awareness on eye care, and hence, there is a huge surge in the demand of ophthalmic products and devices. Given this scenario to continue, the global ophthalmic drug market is expected to grow at approximately 6% over the next couple of years and reach \$21.9 billion in revenues by 2015, with the U.S. claiming a major share of 32.8%. Ophthalmic drug market in emerging economies such as China, India, Mexico and Brazil too will experience a notable growth during the period.



Source: Market Scope

5. Technology Evolution – Never Ending

Since ancient times, delivery of drug to the affected area has been in practice, and it has become an integral part of various medical treatments, including eye. The eye medication delivery method has evolved, resulting in a wide variety of ophthalmic dosage forms existing today. However, eye drops, the conventional dosage forms, continue to be major ophthalmic formulations. But due to changing needs with the onset of different kinds of eye diseases, the demand to create innovative, effective delivery systems surges to achieve better therapeutic results.

A majority of the technology improvements pertaining to ophthalmic medicaments is dosing and drug delivery oriented. Principal focus is on improvements to drop shape and size; upgrades in container closure and filtration; and attempts to develop delivery systems that support preservative-free solutions, as use of preservatives may affect eye health.

In recent times, multi-dose solutions in preservative-free containers are being the major focus of the industry players, due to their commercial viability. Major pharmaceutical companies across the globe are working on their proprietary systems in manufacturing preservative-free medications.

6. Preservative-Free Eye drops – The Currency

Preservative free eye drops, as the name goes, san chemical preservatives. These eye drop formulations evolved due to ocular irritations, disruption of ocular surface, and allergic reactions caused by the preservatives, which are added to micro-bacterial growth and contamination of the drug. Preservative free eye drops are primarily prescribed for people who are susceptible to reactions from preservatives and are ideal for frequent applications. Currently, the ophthalmic market has various preservative free eye drops, as in the below tables, in single-use and multi-use containers, from the leading industry players.

Eye Drops for dry eye syndrome – Single-use (Unit dose)

Product	Company
Systane	Alcon Laboratories
Bion Tears	Alcon Laboratories
Tears Naturale Free	Alcon Laboratories
Soothe	Bausch & Lomb
Refresh Optive	Allergan
Refresh Plus	Allergan
Refresh Celluvisc	Allergan
Refresh Dry Eye Therapy	Allergan
M796thera	Thera Tears
Blink Tears	Abbott Medical Optics
Hydromoor	Moorfields Pharmaceuticals
Lubristil	Moorfields Pharmaceuticals
Vismed	TRB Chemedica

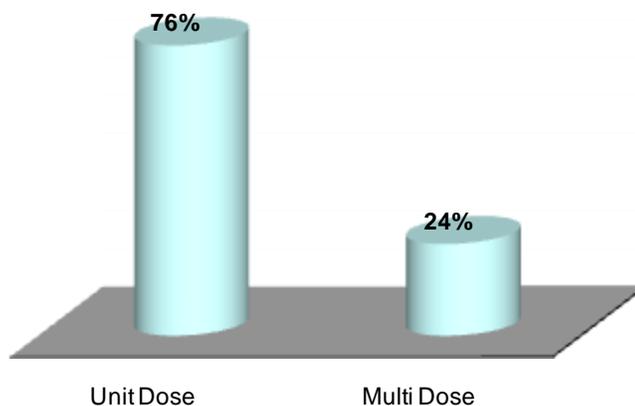
Eye Drops for dry eye syndrome - Multi dose

Products	Company
Vismed Multi	TRB Chemedica (Container-OSD)
Hycosan	Eusan Bausch & Lomb (Distributor) (Container- COMOD system)
Hyabak	Spectrum Thea Pharmaceuticals (Container- ABAK Bottle)
Thealoz	Spectrum Thea Pharmaceuticals (Container- ABAK Bottle)

Eye Drops for glaucoma - Single-use (Unit dose)

Products	Company
Trusopt	Santen Pharmaceutical/Merck & Co., Inc.
Cosopt	Santen Pharmaceutical/Merck & Co., Inc.
Zioptan	Santen Pharmaceutical/Merck & Co., Inc.
Timoptic drops in Ocodose	Aton Pharma

The table above clearly shows that preservative-free eye drops mainly come in single-use (unit dose) vials, due to the possibility of contamination. A comparative analysis on the above listed products reveals that preservative-free multi-dose formulations account for only 24% of the market.



Multi-use containers can help reduce the cost of producing single vials for a prescribed dosage. However, there are challenges in developing preservative-free drops in multi-use containers that can resist bacterial contamination over a period of time. Still, the market is wide open with immense opportunities to explore with the multi-use containers.

7. Multi-Dose Containers - Prevalence

Given the current demand for pharmaceutical companies to produce eye drop dispensers without preservatives, there are few norms that mandates attention. The dispensers should be economical, ensure longest solution shelf life without preservatives, and enable easy use/dispense with precise eye targeting and dispensing amount. They should be easy to assemble, prevent backflow of solutions, and shouldn't vary much in terms of size and weight of the existing dispensers. It is mandate that they should meet FDA requirements, and if recyclable, they will be even more beneficial for the environment.

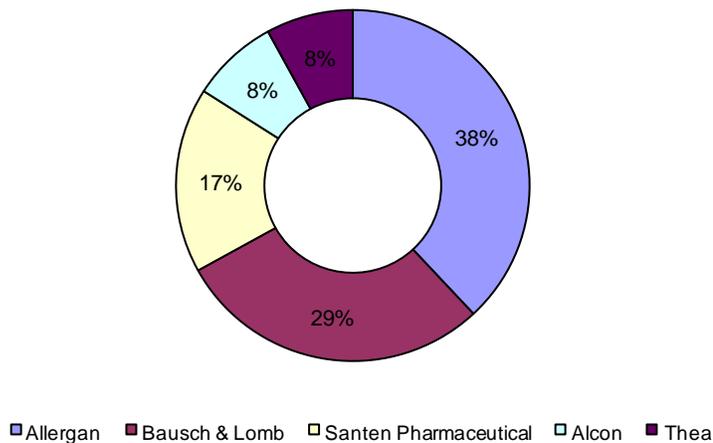
Realizing the market needs, many pharmaceutical companies have designed their proprietary multi-use dispensers:

Company/Laboratory	Product	Details
Rexam	Novelia	<ul style="list-style-type: none"> Patented eyedropper with integrated preservative-free system Features a closing tip system capable of handling drug viscosities up to 1000 m.Pa.s
Rexam	Side actuation device	<ul style="list-style-type: none"> Features a preservative free pump and a closing tip (Developing)
Rexam	Ophthalmic pump system SP570	<ul style="list-style-type: none"> Uses a pump and a special actuator to deliver droplets into eyes tip (Under development)
Spectrum Thea Pharmaceuticals	ABAK	<ul style="list-style-type: none"> A patented preservative-free multi-dose eye drop dispenser Features a 0.2 micron nylon fibre membrane that filters the solution
Aptar Pharma	Ophthalmic Squeeze Dispenser	<ul style="list-style-type: none"> Multi-dose dispenser for unpreserved ophthalmic preparations Ideal for several liquid ophthalmic medications, particularly for chronic conditions such as glaucoma and dry eye
URSAPHARM	COMOD-system	<ul style="list-style-type: none"> Continuous Mono Dose (COMOD) has an integral AIRLESS application system Enables multiple sterile dose delivery of liquid medicinal products
Adelphi Healthcare Packaging	Aero Pump's 3K system	<ul style="list-style-type: none"> Patented system Three-part contamination protection Suitable for both OTC and prescription

Company/Laboratory	Product	Details
		medications
Mystic Pharmaceuticals	VersiDoser and VRx2	<ul style="list-style-type: none"> Enables preservative-free multi-dose Superior dose range (5 µL and greater) Product sterility ensured throughout the “in use” cycle
Pfizer	Airless Antibacterial Dispensing System	<ul style="list-style-type: none"> A multi-dose bottle for the Visine Pure Tears, a preservative-free artificial tears formula Dual-wall reservoir to prevent bacteria from entering the container and contaminating the contents

8. Innovations, Trends and Possibilities

The IP space for preservative-free ophthalmic formulations in unit dose vials is already crowded with numerous innovations. Companies such as Allergan, Bausch & Lomb, Santen Pharmaceutical, Alcon Laboratories and Laboratoires THEA are the leading players in preservative-free aqueous formulations. The figure shows the comparative percentage of patents/publications owned by the said players:



However, with the challenges in preservative-free preparations in multi dose forms and due to its increasing need, companies are focusing on developing different formulations. The widely adopted methods in developing preservative-free multi-dosage formulations are

- Using Disappearing preservatives
- Using Self preserved compositions
- Using containers with antimicrobial application

The technology mainly target on containers that can hold preservative free compositions without contamination. To accomplish the objective, the containers are developed fulfilling various parameters. The commonly adopted technologies to develop preservative-free multi dosage containers are:

- Prevention of backflow
- Airless system/Airtight sealing
- Antibacterial filters
- Precise dispensing
- Longest solution shelf life

9. Scope & Key Players

Preservative-free sterile formulations will be the future trend to avoid hazardous chemicals from active pharmaceutical ingredients (APIs). The challenge for the pharmaceutical companies across the globe is to preserve chemical formulations from bacterial contamination, but without any additives or preservatives. This need opens a wide range of possibilities to innovate novel as well as advance existing approaches, such as

- Disappearing preservatives
- Self-preserved compositions/formulations
- Containers for holding sterile solution
- Dispenser that can absorb preservatives

Relying on the technological advances, many companies have focused on new formulations with preservatives for various ocular therapies, with a clause that they can also be formulated without preservatives and marketed in single use vials. There is a huge potential in IP for new approaches related to preservative-free formulations in multi dosage forms. Pharmaceutical companies who can collaborate with the packaging industry in defining the product specification for the production of preservative free multi dosage formulations can potentially define the market's future.

Key Players

- Allergan
- Alcon
- Bausch & Lomb
- Ciba Geigy Corporation
- Thea Laboratoires
- Santen Pharmaceutical
- Rexam
- Aptar Pharma

10. Conclusion

Due to the adverse effects of preservatives on users and the lack of available multi-dose preservative-free formulations, the ophthalmic pharmaceutical industry has started focusing on replacing preservatives with either single dose vials or less toxic preservatives. Multi-dose dispensing devices will be a cost-effective alternate to manage the life-cycle of preservative-free ophthalmic formulations rather than to invest in single use vials that could incur high productivity cost.

Drug companies are yet to release a multi-dose, preservative-free, user-friendly drug delivery for eye diseases, which can avoid the potential toxic effects of the preservatives used today. Should a solution become available, it is expected to conquer the marketplace, improving patient comfort, ensuring safety and compliance.

Referred URLs:

<http://www.oteurope.com/ophthalmologytimeseurope/Glaucoma+features/Switching-from-preserved-to-preservative-free-pros/ArticleStandard/Article/detail/684992>

<http://www.ncbi.nlm.nih.gov/pubmed/16424520>

<http://www.alleyevision.com/eye-diseases/preservative-free-eye-drops/>

<http://new-glaucoma-treatments.com/preservative-free-eye-drop-for-glaucoma-approved/>

<http://www.marketsandmarkets.com/Market-Reports/ophthalmology-drugs-devices-218.html>

<http://finance.yahoo.com/news/ophthalmic-drugs-world-market-prospects-120000372.html>