



## Ophthalmic Product Development: Key Considerations

Recommendations to Reduce Risks, Mitigate Failure, and Drive Timelines in a Competitive Market

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### **Introduction and Rationale**

The global market value for ophthalmic products was estimated around \$15 billion in 2009 and is expected to increase to over \$20 billion in 2014 (1, 2). An aging population worldwide coupled with higher occurrence of eye conditions and diseases such as diabetic retinopathy, dry eye, glaucoma, and age-related macular degeneration (AMD), have resulted in increased growth in the eye care market (2). The emergence of novel formulations like Restasis<sup>®</sup>, a cyclosporine oil-in-water emulsion formulation, sophisticated dispensing systems such as the Ophthalmic Squeeze Device (OSD - Figure 1), and ophthalmic injections such as Lucentis<sup>®</sup> will inevitably lead to higher expectations and scrutiny from the US Food and Drug Administration (FDA) to gain product approvals.

Currently there are no Guidance Documents from the FDA for in-vitro testing of ophthalmic products. From a Chemistry, Manufacturing and Controls (CMC) standpoint, generics drug developers do not have formal FDA guidelines to successfully develop ophthalmic equivalents to support their Abbreviated New Drug Applications (ANDA). Yet, there seems to be an expectation from the FDA to request more information regarding the CMC attributes of ophthalmic drug products. In the absence of CMC guidelines, it is difficult for the NDA and ANDA applicants to navigate the regulatory process in ophthalmic product development. In addition, there is also a growing expectation for Extractables and Leachables (E&L) testing on ophthalmic products. PQRI plans to release guidelines for PODP (parenteral and ophthalmic drug products) this year, which is expected to increase the testing burden for all stakeholders.

To address the changing regulatory landscape in the ophthalmic area in an effective way, Next Breath proactively developed a comprehensive list of in-vitro analytical testing requirements. This analytical package was developed based on Next Breath regulatory expertise, close collaborations with leading ophthalmic device developers, and ongoing FDA interactions (workshops/conferences).

In this White Paper, Next Breath highlights key considerations and presents strategies to reduce risk and ultimately accelerate the process for gaining approval of an ophthalmic product. It presents a stepwise approach that Next Breath believes is critical in managing the complexities and the unknowns around the development of ophthalmic drug products. It also describes the efforts to support early stage development

through registration stability and batch release. The process described below will assist both the NDA and ANDA applicants in developing robust regulatory packages to gain approval for ophthalmic products.

## **Formulation Development**

An ophthalmic formulation could be a solution, suspension, ointment or an emulsion. A typical eye care product is sterile, nearly isotonic, has some buffering capacity, contains anti-microbial agents (unless the active itself is bacteriostatic) and is packaged into a suitable tamper-evident, multi-dose dispensing system. However, there is a growing trend to invest in multi-dose, preservative free formulations.

During formulation development, the choice of excipients and buffers must be based upon physiological comfort and product stability, and preferably with a proven track record with the FDA. The ideal pH for an ophthalmic formulation is 7.4, equivalent to tear fluid. However, most drugs are chemically unstable at this pH. Therefore a buffer, if included, must facilitate pH as close as possible to the physiological pH, while not causing chemical instability. Thickening agents such as methyl cellulose or hydroxypropylmethylcellulose may be added to prolong the contact time of formulation with the eye surface. Coloring agents are not recommended for ophthalmic products in the United States.

Once the formulation profile is identified, the first step in product development is establishing its physical and chemical attributes such as appearance, viscosity, surface tension, osmolarity and pH. Table 1 provides a comprehensive list of tests that are understood to be expected from the drug developer.

## **Device Selection and Evaluation**

The current standard for ophthalmic medications is either preserved multi-dose configurations or the unpreserved Blow Fill Seal (BFS) single dose preparations which are not easy to handle for elderly patients. For chronic eye care treatment, multi-dose systems are most convenient and cost effective. Patient surveys suggest that they prefer easy, intuitive to use systems that dispense medication in a drop format versus a spray (3). Since eye products are required to be sterile, they must be manufactured under strict aseptic conditions. In the United States, preservatives such as benzalkonium chloride are added to ophthalmic products to minimize/eliminate microbial growth. However, such preservatives are a known ocular irritant, causing eye irritation and allergic response in many patients. Besides causing sensitivity in some patients, there is also increasing concern regarding the toxicity of preservatives and the damage they cause to the eyes over prolonged use (4, 5). Preservative-free formulations are demonstrated to offer a significant medical advantage by reducing ocular damage and discomfort and increasing compliance in glaucoma patients (6). Therefore, the current trend is towards unpreserved multi-dose systems to combine the advantages of both approaches.



Figure 1 – Aptar Pharma's Ophthalmic Squeeze Device (OSD)

To address this clinical need to eliminate preservatives, new devices and technologies have emerged which combine a mechanical tip seal technology with sterile air filtration. The Ophthalmic Squeeze Dispenser (OSD) is an example of novel devices designed to eliminate the need for preservative in the formulation and can be used with existing filling technologies (3). Key advantage of OSD (Figure 1) is the prevention of contamination entering through the tip of dispensing system. The single dose blow-fill seal containers could be filled with preservative- free formulations such as the marketed product Restasis. Mystic Pharmaceuticals' VersiDoser® Ophthalmic Delivery Systems promotes a patient-focused design to facilitate self-administration, ease of use and compliance.

Some researchers have demonstrated in-vitro that preservatives in general and benzalkonium chloride in particular can significantly increase the corneal penetration of the drug, compared to the control formulations. The formulator must take into consideration the impact of omitting the preservatives in the formulation on drug absorption and its surface spreading properties upon administration (7, 8, 9).

The NDA applicant will need to review the advantages and disadvantages of the available devices and identify an appropriate platform to dispense the medication. In addition, formulation composition (particularly the use of preservatives) should be established early in the development in order to make appropriate container selection (glass vs. plastic bottles). For example: glass containers are inert but expensive, plastic containers are cost effective and more commonly used but may interact with the preservatives. There are a limited number of CMOs that offer sterile manufacturing as a service offering, which makes the process further challenging for the drug developer.

Among the various analytical tests that are required of the ophthalmic drug product, an Extractables and Leachables (E&L) study demonstrates the absence of any adverse interactions between formulation and the packaging material. Both NDA and ANDA applicants are required to evaluate E&L profile for all container closure systems. Leachable studies are particularly relevant during stability studies (Table 1).

As part of the device screening and selection process, simulated “patient factors” need to be considered and should be representative of human use conditions. For example, the force applied to the bottle as well as the angle of orientation during dosing may affect the size of the droplet formed, which ultimately may affect the dispensed dose. Figure 2 illustrates how the weight of a drop can be affected by the angle of administration for four different ophthalmic formulations. These studies can be used to support selection of appropriate device closure system.

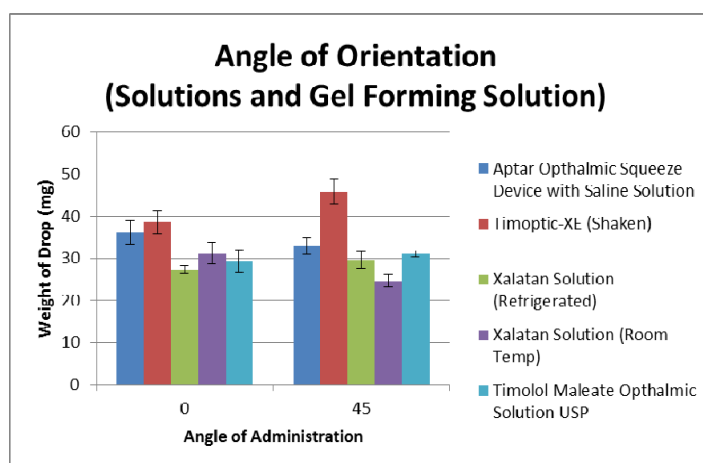


Figure 2 - Angle of Orientation vs. Weight of Drop

Additional analytical techniques such as high speed photography to capture droplet size during dispensing could be performed to assist in formulation development and device optimization. For finished products containing multiple doses, emitted dose through container life (beginning, middle and end of life through label claim) will need to be performed. Shaking studies to establish consistent dosing profile for multi-dose suspension formulations may be necessary.

## **Key Analytical Considerations**

### ***Particle Size and Dissolution***

Particle size influences the rate and extent of dissolution as well as eye irritation in case of suspension and emulsion formulations (10). In general, particles <10 µm are recommended for ophthalmic suspension formulations to facilitate patient comfort and minimize damage to cornea. In order for the deposited drug particles to be useful, the dissolution rate is even more critical for a slowly soluble substance in relation to its residence time in the eye (10, 11).

There are no approved guidelines or published methods that describe the dissolution/release of drug from an ophthalmic suspension or emulsion. Various studies have been published using conventional dissolution testing apparatus without definitive outcomes. Equipment such as the USP Apparatus 4 modified for ophthalmic application could be used to develop and validate methods to generate drug dissolution profiles.

### ***Ocular Irritation Studies***

Ocular Irritation studies will need to be performed to establish that the active pharmaceutical ingredient (API) and the excipients in the formulation will maintain adequate comfort levels for the patients (12). Ocular irritation testing can be conducted using the MTT ET-50 method (time of exposure needed for a formulation to reduce the viability to 50% of control tissues) or with human cell-derived in-vitro corneal tissue model. Several of these are commercially available and claim to provide an in-vitro alternative to the Draize rabbit eye test (13).

### ***In Vitro Comparability: Generic Ophthalmic Drug Products***

In addition to the tests described above for the NDA applicant, there are further considerations for the ANDA applicant. During generic product development process, ANDA applicant must determine that the Test product (generic formulation + dispensing system) is comparable to the marketed Reference Listed Drug (RLD). It is important that ANDA applicant understands the Innovator's dispensing system in the generic

context during method validation. ANDA applicant will need to compare results from Test and RLD products and demonstrate that the Test product is qualitatively and quantitatively equivalent (Q&Q) to the RLD. A comparative approach may be taken for the final analysis based on population bioequivalence statistics.

Next Breath highlights the comparative in vitro tests for ophthalmic (ANDA) applicants in Table 1. In the absence of FDA guidance for in vitro bioequivalence requirements, these tests may be considered supportive of the in vivo studies that are required for solution and suspension formulations. The tests shown in Table 1 may be relevant for solution, suspension, gels and emulsion formulations. In addition, long term stability study is expected to be performed by the ANDA applicant.

### **Stability Program**

A robust stability program will need to be performed to establish stability of the ophthalmic drug product. Long-term storage condition of 25°C/40% RH and Accelerated condition of 40°C /20 to NMT 25% RH could be considered. Crystal growth and agglomeration will need to be monitored for suspension formulations and likewise any evidence of breakdown in emulsion formulations. In addition, CMC tests (Table 1) on stability, including preservative content, if used, and microbiological testing, may need to be performed. Critical parameters such as drug release or gel strength may need to be analyzed during stability studies. Next Breath recommends the inclusion of Leachables testing as part of the stability program (assuming the extractables were identified early in the product development). The proposed stability studies are applicable to both NDA and ANDA applicants.

### **Batch Release**

The following scope is proposed to be considered for clinical and finished product batch release for ophthalmic drug products. ANDA applicants will need to perform some of the tests below to show comparability to the RLD.

<b>*Test</b>	<b>Development</b>	<b>Irritation</b>	<b>In Vitro Comparability</b>	<b>Stability</b>	<b>Batch Release</b>
Drop Weight	X		X	X	X
Refractive index	X	X			
EpiOcular model	X	X			
pH	X	X	X	X	X
Osmolarity	X	X	X	X	X
Viscosity	X		X	X	X
Surface tension	X		X	X	X
Assay	X		X	X	X

Related substances/impurities	X			X	X
Appearance	X			X	X
Turbidity	X			X	X
Drug content per drop	X		X		
Foreign particulate matter				X	X
Particle size by microscopy	X		X	X	X
Globule size	X		X		
Zeta potential	X		X		
Drug release by dissolution	X		X		
Partitioning by ultracentrifugation	X		X		
Gel-strength	X		X		
Leachables				X	

Table 1: Outline of Analytical Methods for Ophthalmic Drug Products \*Preservative content and microbiological testing are not included but recommended.

## **Conclusion**

The increased scrutiny by the regulatory agencies and the growing market share for ophthalmic products are expected to rise sharply in the coming years. The complexities in the formulation, device design, performance, and absence of FDA guidance present a number of unique challenges as well as opportunities for the NDA and ANDA applicants in the development and commercialization of ophthalmic products. Preservative agents such as benzalkonium chloride are seen higher scrutiny from regulators. Avoiding such agents constitutes new challenges and adds complexity; however it also offers new opportunities in terms of drug tolerance.

This white paper attempts to shed some light on the complexities surrounding ophthalmic product development. It is our judgment that if the drug developer follows a stepwise approach focusing on the key considerations discussed above and moves to the next phase only if a “Go, No - Go” decision is achieved, the development process will become more manageable.

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