OPHTHALMIC PRODUCT DEVELOPMENT: REDUCE RISKS, MITIGATE FAILURE & DRIVE TIMELINES IN A COMPETITIVE MARKET

In this technical white paper, Badre Hammond, MBA, Associate Director, Business Development at Next Breath, LLC, together with Shailuja Somaraju, PhD, Vice-President, and Julie Suman, PhD, President, highlight key considerations and present strategies to reduce risk and ultimately accelerate the process for gaining approval of an ophthalmic product, with a focus on the US. The authors present a stepwise approach that Next Breath believes is critical in managing the complexities and the unknowns around the development of ophthalmic drug products. They also describe the efforts to support early-stage development through registration stability and batch release. The process described below will assist both NDA and ANDA applicants in developing robust regulatory packages to gain approval for ophthalmic products.

INTRODUCTION AND RATIONALE

The global market value for ophthalmic products was estimated around US$16.9 billion (£10.2 billion) in 2012 and was expected to increase to more than $20.2 billion in 2017.[1] 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 Restastis®, a cyclosporine oil-in-water emulsion formulation, sophisticated dispensing systems such as the Ophthalmic Squeeze Device (OSD; see Figure 1), and ophthalmic injections such as Lucentis® will inevitably lead to higher expectations and scrutiny from the US FDA as their developers seek product approvals.

Currently there are no guidance documents from the FDA for *in vitro* testing of ophthalmic products. From a CMC standpoint, generics drug developers do not have formal FDA guidelines to support their development of ophthalmic equivalents and the associated ANDAs. 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. Product Quality Research Institute (PQRI; Arlington, VA, US) released guidelines for PODP (parenteral and ophthalmic drug products) last year, which increase the testing burden for all stakeholders.[3]

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

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

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*Test	Development	Irritation	In Vitro Comparability	Stability	Batch Release
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	

Figure 2: Table outlining analytical methods for ophthalmic drug products. *Preservative content and microbiological testing are not included, but recommended.

analytical package was developed based on Next Breath's regulatory expertise, close collaborations with leading ophthalmic device developers, and ongoing FDA interactions (workshops/conferences).

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 hydroxypropyl-methylcellulose may be added to prolong the contact time of formulation with the eye surface. Colouring agents are not recommended for ophthalmic products in the US.

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. Figure 2 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.[4]

Since eye products are required to be sterile, they must be manufactured under strict aseptic conditions. In the US, preservatives such as benzalkonium chloride are added to ophthalmic products to minimise/eliminate microbial growth. However, many such preservatives are known to cause 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 with prolonged use.[5,6] It has been demonstrated that preservative-free formulations offer a significant medical advantage by reducing ocular damage and discomfort and increasing compliance in glaucoma patients.[7] Therefore, the current trend is towards unpreserved multi-dose systems to combine the advantages of both approaches.

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 a class of novel devices designed to eliminate the need for preservative in the formulation and which can be used with existing filling technologies.[4] Key advantage of OSD (Figure 1) is the prevention of contamination entering through the tip of dispensing system. The single-dose BFS containers could be filled with preservative- free formulations such as the marketed product Restasis. Mystic Pharmaceuticals' VersiDoser® ophthalmic delivery system promotes a patient-focused design to facilitate self-administration, ease of use and compliance. Individual liquid doses are contained within blister packaging with each blister having a proprietary, single-use Vjet™ dispensing nozzle.

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 with 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.[8,9,10]

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 *versus* plastic bottles). For example, glass containers are inert but expensive, whilst 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.

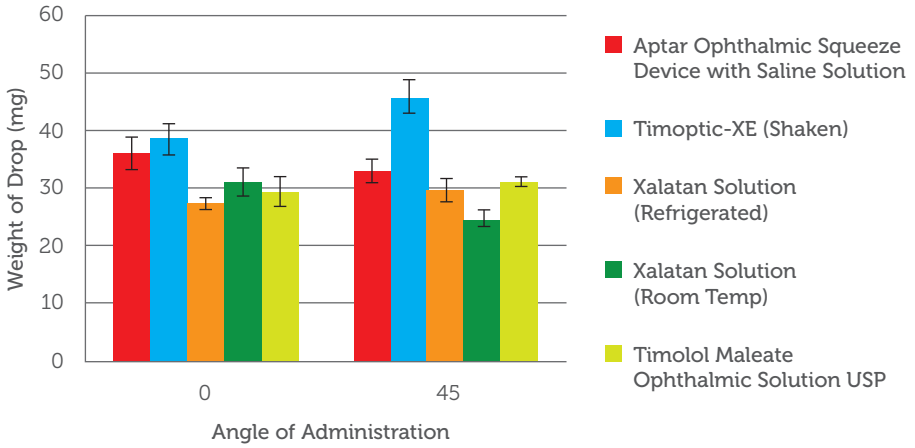

Figure 3: Graph showing Angle of Orientation versus Weight of Drop Dispensed (mg) for various ophthalmic products.

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 (Figure 2).

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 3 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.

Additional analytical techniques such as high-speed photography to capture droplet size during dispensing could be performed to assist in formulation development and device optimisation. 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 for suspension and emulsion formulations.[11] In general, particles <10 µm are recommended for ophthalmic suspension formulations to facilitate patient comfort and minimise 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.[11,12]

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 API and the excipients in the formulation will maintain adequate comfort levels for the patients.[13] 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.[14]

In Vitro Comparability: Generics

In addition to the tests described above for the NDA applicant, there are further considerations for the ANDA applicant. During generic product development process, the

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 the ANDA applicant understands the innovator's dispensing system in the generic context during method validation. The 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.

We highlight the comparative *in vitro* tests for ophthalmic (ANDA) applicants in the table in Figure 2. 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 Figure 2 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 conditions of 25°C/40% relative humidity (RH), and accelerated conditions 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 (see Figure 2) 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 analysed 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 scope in Figure 2 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.

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 commercialisation of ophthalmic products.

Preservatives such as benzalkonium chloride are receiving closer scrutiny from regulators. Avoiding such agents brings new challenges and adds complexity. However, it also offers new opportunities in terms of drug tolerance.

This 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 here, and moves to the next phase only if a "go/no-go" decision is achieved, the development process will become more manageable.

"Formulation composition, particularly the use of preservatives, should be established early in the development in order to make appropriate container selection (i.e. glass versus plastic bottles)"

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