

# Key Challenges to US Topical Ocular Drug Development



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The diverse products in the eye industry include contact lenses and lens care solutions, OTC drops for a wide range of applications, diagnostic modalities, surgical products, systemically administered drugs and prescription topical eye products.

Although the market size for ocular drugs and eye care products is estimated to reach more than \$12 billion (US) by 2010,<sup>1</sup> few new ocular drugs are being created. There appears to be a chronic lack of innovation in the ocular drug development arena, despite the large market potential. For example, the FDA website notes that only 21 ocular drugs were approved in the last 10 years; 30 new drugs if one looks back to 1995. No ocular drugs were approved in 1995 or 2003. Two manufacturers, Alcon and Allergan, garnered the most approvals during this timeframe.<sup>2</sup>

For such a large market, there have been a limited number of traditional players (e.g., Alcon, Allergan, Bausch and Lomb). However, things may be changing. A top-line review of ClinicalTrials.gov reveals that a plethora of other players (e.g., ISTA, Innovative Medical, Chakshu Research Inc., Vistakon, Novartis, Pfizer, Inspire, Othera, Merck, Glaukos Corp., Danube Pharma, Santen Oy and Sirion)<sup>3</sup> are finding the barriers low enough—and the potential profit large enough—to enter this arena. The spectrum of companies in this space includes the largest players, which can develop and market their own drugs, and smaller entities that rely on in-licensing to fuel their product pipelines. The smaller players in this arena have benefited from research and development talent developed by the larger ophthalmic companies such as Alcon, Allergan and Bausch and Lomb. Some companies have directly benefited from academic research.

The baby boomers will positively impact ophthalmic clinical research because, as they continue to age, the incidence of many common age-related eye diseases is predicted to increase. In addition, new innovations will increase the market size by making previously untreatable conditions (e.g., dry

macular degeneration, multiple ocular inflammatory diseases) amenable to therapy.

If these assumptions are correct, why have more products not been developed in this potentially lucrative—and growing—market?

To help answer these questions, based on recent experience in topical ocular drug development, this article examines five key facets of the topical ocular drug industry to highlight key challenges associated with ocular drug development.

- An understanding of ophthalmology and the scientific requirements for topical ophthalmic drugs and devices
- Development and manufacturing of ophthalmic drug products
- Knowledge of US ophthalmology regulatory requirements
- Overall clinical drug development issues
- A thorough knowledge of ophthalmology clinical trial design and conducting clinical trials that meet regulatory guidelines

## Scientific Requirements

The eye is a highly complex organ and several of the ocular structures, such as the retina and optic nerve, are nonregenerative. As such, ocular drug development requires a thorough understanding of ophthalmology, the associated eye structures, pathophysiology, the genetic makeup of ocular diseases and a solid knowledge of the ability of the eye to respond to physical and pharmacologic intervention.

For topical drug development, a thorough understanding of drug formulation, the permeability factors of the ocular surface (cornea, conjunctiva and sclera) and appropriate tissue targeting is required. Due to its inability to regenerate and its lack of reserve capacity, the eye is considered a “high stakes” organ.

**Figure 1** displays a cross section of a human adult eye and its main anatomical structures; anterior and posterior segments are highlighted.

Ocular drug delivery can be divided into



three categories: topical, which typically targets the anterior segment; intraocular/intravitreal, which typically targets the posterior segment; and systemic, which can be used to treat conditions in the anterior and posterior segments of the eye. Because systemic ocular delivery could be utilized to treat topical eye disease, only systemic and topical ocular drug delivery will be discussed.

### **Topical**

Topical drugs are those that can be applied to the ocular surface. These drugs typically take the form of liquids, gels or ointments, each with benefits and drawbacks. Topical treatments are effective in delivering drugs to the ocular surface and anterior segment of the eye. However, they are not particularly effective in treating conditions involving the posterior segment because it is difficult to deliver therapeutic drug levels to the posterior segment of the eye using this route of administration. Common diseases treated with this route of administration include glaucoma and anterior infections and inflammation.

### **Systemic**

Systemic administration refers to oral, intramuscular or intravenous administration of drugs to treat ophthalmic diseases (e.g., high dose intravenous steroids used to treat uveitis). The disadvantage of systemic administration is that the entire body will be exposed to these drugs with side effects that can impact quality of life and be potentially dangerous.

Most conditions affecting the ocular surface and anterior segment can be treated effectively by topical delivery. The main limitations are poor penetration (<5%), rapid tear washout and poor patient compliance.<sup>4</sup>

To address these topical limitations, companies are applying more-recent advances in research to topical drugs. These advances are improving the benefit-risk ratio by optimizing drug activity at the target site while significantly reducing local and systemic side effects. One technique is called soft drugs. These are new, active therapeutic agents with a chemical structure specifically designed to allow predictable metabolism into inactive metabolites after exerting the desired therapeutic effect. In other words, these compounds produce their treatment effects and then are rapidly inactivated metabolically to reduce side effects. Examples include:

- Adaprolol maleate—a beta-blocker with excellent intraocular pressure reduction

and reduced cardiovascular and pulmonary side effects

- Oteprednol etabonate—a steroid that has been approved for anti-inflammatory treatment of the ocular surface with significantly lower cataractogenic and ocular hypertensive effects<sup>5</sup>

## **Development and Manufacturing of Topical Ophthalmic Drug Products**

For topical ophthalmic drug development, hurdles to improving bioavailability include: lacrimal drainage; reflex blinking; drug dilution by tears; rapid turnover; limited permeability of the cornea; and rapid elimination of the drug through the lacrimal system.<sup>5</sup> Commonly, the small ocular surface cannot retain the entire drop of medication and the vast majority of each drop is lost as a “tear” on the patient’s face. Several strategies are used to overcome these hurdles:

- using high concentrations of the drug to overcome tear dilution and improve the effective dose delivered into the eye
- using gelling agents or mucoadhesive polymers to increase contact time and increase ocular penetration (this also may allow for less frequent dosing)
- matching pH as closely as possible to the tear pH to reduce stinging and tearing
- customizing the formulation (such as increasing lipophilicity) to maximize penetration of the cornea, conjunctiva and sclera

As if physical limitations were not enough, there are also several challenges when manufacturing ophthalmic drug products. These products must be manufactured and packaged using sterile techniques and the number of facilities that are GMP compliant for ophthalmic preparations is limited. For the formulation of aqueous ophthalmic solutions, many critical factors must be taken into consideration such as:

- “appropriate salt of the drug substance
- solubility
- therapeutic concentration required
- ocular toxicity
- pKa
- effect of pH on stability and solubility, pKa
- tonicity
- buffer capacity
- viscosity
- compatibility with other formulation ingredients and packaging components

- choice of preservative (antimicrobial)
- ocular comfort
- ease of manufacturing<sup>6</sup>

The pH of the dosage form should be within physiological range in order to avoid eye irritation, which has its own consequences including ocular discomfort and drug dilution from excessive tearing (a natural response). Proper buffer capacity can positively impact the bioavailability of the drug as well as ocular comfort.<sup>6</sup>

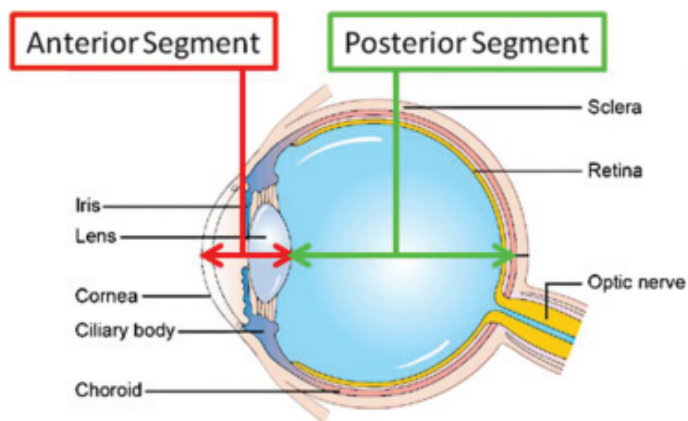
Suspensions are another form of popular topical ophthalmic drugs. One of the advantages of some recently developed suspensions is that some of the drugs are hydrophobic and hence have limited solubility in water. In order to be delivered effectively, these drugs must be placed in a water-based suspension so they will be absorbed in the tear film in suspended form. These products are complex and require scientific “understanding of interfacial properties of chemicals, wetting, particle interaction zeta potential, aggregation, and sedimentation.”<sup>6</sup> The need for buffers and preservatives for suspensions is similar to that for ophthalmic solutions. However, compatibility of these chemicals with flocculating systems must be kept in mind. Key issues of concern with suspensions include aggregation of particles, sedimentation and caking. It should also be noted that suspension products are not thermodynamically stable and storage temperature can be important.<sup>6</sup>

For prolonged therapeutic actions, especially during nighttime, ointments were generally the product of choice until the recent advent of gels and mucoadhesive polymer systems. The major disadvantage of ophthalmic ointments is blurred vision. Important factors in developing this dosage form are: utilizing ingredients that are not irritating to the eye, uniform ointment consistency that forms a uniform thickness over the eye; and ensuring it does not cause excessive blurring.

Mucoadhesive polymers are ideal for providing localized delivery of an active ingredient to a specific site in the body, such as an eye. The bioadhesive properties of these polymers improve delivery of the drug by increasing contact duration and bioavailability. To optimize the drug’s release kinetics at the local site, the choice of the correct polymer is crucial. Some examples of drug products using bioadhesive polymers are timolol gel forming solution, Timosan in Europe, and Betoptic S in the US.

There are also nonconventional topical drug delivery systems including nonerodible ocular inserts, prodrugs, microspheres and

Figure 1. Cross Section of a Human Adult Eye Highlighting Anterior and Posterior Segments



nanoparticles. However, each has limitations. For example, nonerodible ocular inserts—with controlled release pilocarpine—have limited utility as they have to be inserted and removed weekly. Further, the drug has a higher level of side effects than topically applied drops. Prodrugs, such as Dipivefrin (a prodrug of epinephrine) and Othera’s OT-730 (a prodrug beta-blocker for glaucoma) have been formulated to be selectively metabolized into the active metabolite in the target tissues. These ocular drugs may have better safety profiles than their systemic cousins, including increased bioavailability, higher potency, improved chemical stability and prolonged duration of action.<sup>7</sup> As a result, a smaller amount of the drug is required, which potentially decreases local irritation and other side effects. Compared with conventional ophthalmic drugs, the manufacture of sterile microspheres and nanoparticles is more complicated. These dosage forms, however, offer an exciting avenue for ocular drug delivery that is still evolving.<sup>6</sup>

### US Regulatory Requirements

There are currently no official regulatory guidance documents from the US Food and Drug Administration (FDA) for topical ophthalmic drug development.<sup>8</sup>

Fortunately, much of the information available for preclinical and clinical drug development is also applicable to ophthalmic drug products. Much information can be garnered from historical data from the summary basis of approvals (sometimes also referred to as a product review) of currently marketed ophthalmic drug products, available to the public through the *Freedom of Information Act*.



Information from package inserts for approved drugs are another source of information.

A better approach, however, is to develop a robust drug development plan based on publicly available information and consultation with experts in this area of specialty. The next step is to meet with the regulatory authorities early to garner buy-in for the initial drug development plan. For ophthalmic products, particular importance is placed on efficient preclinical development and the pre-IND and subsequent meetings with FDA. Drugs for ophthalmic use in the US are regulated by FDA's Division of Anti-Infective and Ophthalmic Products. The advisory committee that provides expert opinions for New Drug Application approval of these products is the Dermatologic and Ophthalmic Drugs Advisory Committee.

Nonclinical development for novel ocular drugs is not well defined. Nonclinical safety assessment of the drug is crucial to protect subjects participating in clinical trials, hence an overall risk assessment for humans is required.<sup>9</sup> It is crucial that a thorough assessment be conducted to ensure that the proper species are selected for testing and that the study design is robust, including adequate

morphological evaluations.<sup>9</sup> If the drug—particularly a novel ocular drug—has not been previously studied, ocular route studies in two species (typically nonrodents) are preferred by regulatory authorities. One species may be sufficient with proper justification, especially in cases of lack of biologic homology in other species.<sup>9</sup> Of course, it is best to gain FDA buy-in at the pre-IND stage.

Ocular pharmacokinetic studies, usually in one species, are needed to examine the absorption, distribution, metabolism and excretion of the drug in the various ocular compartments. Another type of study generally needed is ocular tolerability of the drug, including irritancy. These studies are customarily conducted in rabbits. Systemic toxicokinetic studies are needed only if systemic tissues are evaluated. Ocular toxicokinetic studies are generally not needed. Systemic toxicity studies via another route of administration such as intravenous or oral are required in one species. In vitro genotoxicity tests are also required to look at chromosomal mutations and clastogenicity.<sup>9</sup>

While a pre-IND meeting and a meeting towards the end of Phase 2 development are standard in drug development, more frequent communication with the agency is recommended to ensure that the development program is in line with FDA guidelines. It is also a good idea to have the Division of Anti-Infective and Ophthalmic Products review the protocols for all pivotal studies prior to obtaining IRB approval and starting clinical trials. This will ensure that all FDA requirements are addressed. For example, in glaucoma treatment, certain compounds must show significant treatment effects at specific time points. If these are not incorporated into the research design, the drug development timelines may be significantly impacted, as the company may have to repeat the trial or reanalyze existing data.

## Overall Clinical Drug Development Issues

Development plans for topical ophthalmic drugs tend to be simpler and less costly than for many systemic drugs. It is easier to establish the safety and efficacy of topical products partly because they are associated with fewer adverse events (AEs) and serious adverse events (SAEs). While topical products could have serious complications, the majority of these compounds fail due to a lack of efficacy rather than safety concerns. When failure is not due to lack of efficacy, it is usually related to a lack of anterior segment tolerance rather than significant AEs or SAEs.



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In view of these advantages, what accounts for the lack of a robust topical ophthalmic drug development industry? Possible key reasons include:

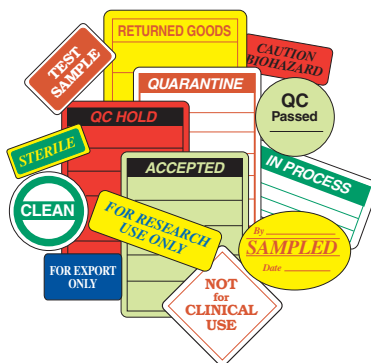
- The lack of regulatory guidance may have created a barrier to entry into ophthalmic drug discovery. The lack of skills and experience can be intimidating in the high-stakes business of clinical research and may dissuade companies and individuals from entering this industry.
- The ophthalmology drug development pipeline has not had the same success as other therapeutic areas in developing blockbuster drugs (although this is changing with Restasis and some other compounds with large potential markets, such as macular degeneration).
- Many topical products achieve only modest financial success (e.g., <\$50 million US). However, this may be changing due to the increased incidence in many ophthalmic conditions associated with expansion of the elderly population, the recent financial success of several topical ocular drugs and the realization that novel therapeutics and innovation command a premium price.
- Ophthalmology requires a unique set of capabilities and experience that is limited to a small number of physicians, research professionals and business professionals (discussed below).
- Research to discover new topical products is costly. As a result, some US companies have taken the approach of in-licensing non-US products with known safety and efficacy profiles that require limited drug development and less risk to become approved in the US. Other companies have experimented with different formulations or delivery systems that avoid patents and offer an advantage over existing therapies. These companies can reduce the overall development cost by using the 505(b) (2) pathway.

### Clinical Trial Design and Implementation Issues

While there is no paucity of clinical ophthalmologists, those with significant drug development experience are rare. Most ophthalmic drug development companies are run by experienced clinical

research professionals who have gravitated to ophthalmology—but they may not have specific training in ophthalmology drug development, much less board certification in this specialty. When one considers the number of ophthalmologists with research experience, board certification and entrepreneurial zeal, the field becomes extremely limited. As if this were not enough, consider the financial disincentive of drug development for ophthalmologists in private practice. Ophthalmology provides some of the few remaining elective, “cash up front” procedures remaining in medicine (LASIK or blepharoplasty). Therefore, time spent participating in clinical trials can cut significantly into a physician’s net income. Another ophthalmology drug development challenge arises from the need for clinical acumen garnered from experience, including use of specialized equipment, proper use and interpretation of cutting-edge technology and work with “reading centers” used in ophthalmology trials (similar to ECG core laboratories used for cardiovascular trials). Ophthalmology training is

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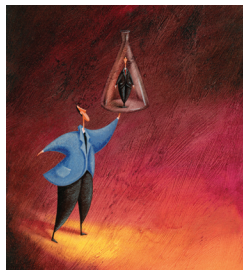


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not part of the general medical training of physicians and other professionals and this means that, in general, only people with this specialty training have the necessary specialty experience.

In this specific therapeutic area, sites should be selected based upon their research experience and clinical ophthalmology experience. Familiarity with ophthalmology research for efficient site selection and start-up—coupled with the ability to speak the ophthalmology drug development language—is critical to the success of the trials.

In order for the drug development process to be efficient, all parties must possess experience in clinical ophthalmology and ophthalmic research. This combination is rare.

A thorough understanding of cutting-edge technology used in ophthalmology studies is also critical. These technologies, while adding complexity, have allowed more objective and reproducible outcome measures. Technologies such as optical coherence tomography, scanning laser ophthalmoscopy, high-resolution ultrasound, newer-generation corneal topographers, corneal pachymeters and others deliver more-precise, repeatable measurements, which help create robust and reproducible clinical research results.

Ophthalmology reading centers have standardized processes to evaluate and interpret the results created at the sites. Precise results from new technologies gathered at the research sites combined with standardized interpretations of reading centers have improved clinical research results of ophthalmology trials. These reading centers are increasingly solicited by FDA.

## Summary

- There is a gap between the number of products in ophthalmology pipelines and the potential market.
- The eye industry has suffered from a lack of innovation in the past decade.
- Lack of regulatory guidance may be a contributing factor.
- Lack of emphasis by large CROs created a void in the type of ophthalmologic drug and device development expertise that is commonly available for other, more traditional therapeutic areas.
- More-lucrative products have recently been developed in the topical eye industry and this trend will likely continue as innovators seek to enter this attractive market.
- Experience managing and conducting

ophthalmic clinical trials (whether in-house or outsourced) is critical to successful ophthalmic drug development.

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## Figure

Cross Section of a Human Adult Eye with the anterior and posterior segments. Image from [www.cancerhelp.org.uk/help/default.asp?page=18544](http://www.cancerhelp.org.uk/help/default.asp?page=18544). Accessed 25 January 2009. Anterior and posterior segment labels added by the authors.

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