Preclinical Pharmacokinetics Targeting for Ophthalmic Drugs

The ophthalmic medical product market continues to grow at a strong pace, from approximately $12 billion in 2010 to an estimated $52.4 billion in 2017. In large part, this growing market is fueled by the aging world population, as older individuals consume more ophthalmic medical products. Feeding into this large and growing market, demand for preclinical testing services is robust, but these programs are not “run of the mill” and require considerable expertise as described below. While a distinct regulatory pathway does not exist within the United States Food And Drug Administration (US FDA) for ophthalmic drugs, there are certain preclinical testing programs they typically go through prior to regulatory approval to begin clinical trials. Consequently, selecting the right outsourcing partner for these critical testing programs is of the utmost importance.

One of the most decisive preclinical testing programs for ophthalmic drugs is ocular pharmacokinetics, or PK. From a high-level perspective, ocular PK studies help elucidate a compound’s absorption into, distribution and metabolism within, and elimination from the eye (ADME). More precise objectives for these studies typically center on determining a compound’s ability to get to the target tissue, and in what concentration, by a specified dosing method. These studies often come relatively early in development and can be combined with efficacy studies (not only is the drug present, but is it present at a therapeutic concentration in the target tissue). Ocular PK studies can play an enormous role in the ophthalmic drug development process as they can help clarify which drug delivery methods (e.g., topical, intravitreal, subconjunctival, systemic) allow for optimal drug penetration into the ocular tissue of interest.

* For the purposes of this paper, this includes drug-eluting devices.
Albino (New Zealand White) rabbits are generally the species of choice for preclinical ocular PK testing. When there is a concern that an ocular compound may bind to melanin, comparative PK studies may be done in species with pigmented eyes, such as Dutch Belted rabbits. Many innovators perform in vitro melanin binding studies to determine if this is a potential consideration for the in vivo studies. Species with larger eyes, such as pig or sheep, may be needed when large drug delivery devices are tested or larger volumes of tissue are needed. Some drug development programs start with rodent PK work primarily to decrease costs and use less of the active pharmaceutical ingredient (API), but in Absorption Systems’ experience the limited volume of tissue may result in the need for additional animals or an inability to harvest all of the ocular tissues of interest. All animals should be pre-screened to ensure that there are no ocular abnormalities present at the beginning of the study. Unless otherwise directed by a drug regulatory agency, ocular PK is usually performed in just one mammalian species.

The decision on which tissues to collect, and how, will dictate the level of expertise needed to perform an ocular PK study. As a complex organ, the eye contains several distinct tissues. Collecting all of the tissues requires attention to detail and exemplary knowledge of ocular anatomy. In addition, the collection of certain tissues (e.g., the trabecular meshwork, which is of great interest in PK studies for intraocular pressure-lowering (anti-glaucoma) compounds), necessitates a high level of expertise at fine tissue micro-dissection due to their small size and delicate nature. For some compounds and drug delivery methods (e.g., intravitreal injection), subsectioning the vitreous humor, choroid, and retina into quadrants may be utilized to monitor the distribution of the compound after administration. Depending on the nature of the compound, the globe may need to be flash-frozen, and frozen tissue layers removed later, to preserve the parent compound and arrest the formation of metabolites prior to tissue dissection. A delay of even the few minutes it takes to dissect the tissues may result in poor compound levels if metabolism continues after globe removal. On the other hand, tissues may go unfrozen during dissection when there are no concerns about the chemical or metabolic stability of a compound.

Care must also be taken to ensure that cross-contamination does not occur during dissection. Without a procedure in place to ensure that tissues are completely dissected and freed from one another, and that instruments are cleaned in between, contamination may occur, which can compromise the integrity of the study. This is especially true for compounds that are administered topically, where the highest concentrations are likely to be found in the front of the eye. Weights of the tissues should be obtained both at harvest and prior to bioanalysis, to account for any dehydration.
High-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) is used to quantify concentrations of test compounds in the various ocular compartments down to the ng/mL or pg/mL level. Sample preparation techniques must be optimized to account for the small volumes of tissues obtained and the low level of compound present in some of the tissues. These techniques include dilution and homogenization with organic solvent, protein precipitation, solid-phase extraction, and liquid-liquid extraction. To minimize cost and reduce the number of animals required for blank matrix, composite ocular matrices are often used to prepare calibration standards. Absorption Systems uses two composite ocular matrices for bioanalysis – 1) combined aqueous and vitreous humor for analysis of the humor matrices, and 2) a homogenate of the remaining ocular compartments for analysis of the solid tissues. Process efficiency is evaluated to confirm acceptability of these surrogate matrices for analysis of incurred samples. Analytical rigor can vary, depending on the stage of development, and may include linearity, sensitivity, accuracy, and precision of the method, along with stability assessments in each of the ocular tissues. For prodrugs, both the parent and active forms of the test compound are quantified, and the rate of conversion of the former to the latter may be evaluated in vitro to determine the optimal collection procedures for the in vivo study (e.g. freezing, acidification, or other treatment of collected tissues). GLP-compliant bioanalysis may be performed if required for regulatory submission.

### References


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