Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Moxifloxacin Solution Case Study

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PURPOSE

• Development of generic ophthalmic drug products is challenging due to the complexity of the ocular system and a lack of sensitive testing tools to evaluate its interplay with pharmaceutical formulations.

• Identifying the impact of any differences in manufacturing, formulation, or physicochemical characteristics between a generic ocular drug product and its reference listed drug product is critical to maintain safety and efficacy for patients.

• Due to their poor sensitivity, associated costs, and ethical limitations, comparative clinical endpoint bioequivalence (BE) studies for a generic ocular drug product are a significant challenge to pharmaceutical industry.

• The purpose of this research is to demonstrate the value of ocular mechanistic absorption models (MAM) linked to physiologically based pharmacokinetic (PBPK) models validated against rabbit pharmacokinetic (PK) data to predict clinical ocular exposure.

OBJECTIVE

• To develop and validate a MAM-PBPK for moxifloxacin (Mox) administered as an ophthalmic solution in rabbits.

• To predict Mox clinical ocular exposure following topical administration in patients undergoing cataract, vitrectomy, and keratoplasty surgeries.

METHODS

• All simulations were performed using GastroPlus® (Version 9.8.2 Simulation Plus Inc., Lancaster, CA, USA).

• Ocular Componental Absorption and Transit (OCAT™) model was used to build a MAM for Mox ophthalmic solution. The OCAT model accounts for nasolacrimal drainage, ocular absorption, and distribution in the eye.

• Cornea epithelium and aqueous humor permeabilities as well as melanin binding were optimized to capture rabbit data. External validations were performed using five additional ocular PK datasets in rabbits.

• The OCAT model was subsequently used to predict Mox exposure in humans by adjusting the physiological parameters to match human ocular physiology. All of Mox specific parameters were kept constant between rabbit and human simulations.

CONCLUSION

• Preliminary data suggest that the OCAT model reasonably predicts human ocular exposure once validated with rabbit ocular PK data for Mox ophthalmic solutions.

• The model reasonably predicts observations sampled from patients with cataract, vitrectomy, and keratoplasty surgeries.

• Due to the significant intersubject and interstudy variability in observed human ocular exposure, extrapolation from more case studies is necessary to validate the MAM-PBPK extrapolation method.

• Successful clinical extrapolation of Mox ophthalmic solution represents an important step in validating the use of MAM-PBPK models for prediction of human ocular exposure for ophthalmic drug products.

• The approach described in this study is expected to have a significant impact on ophthalmic generic drug product development.

REFERENCES

This project is funded by the U.S. Food and Drug Administration: grant number: 1U01FD006927.

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