

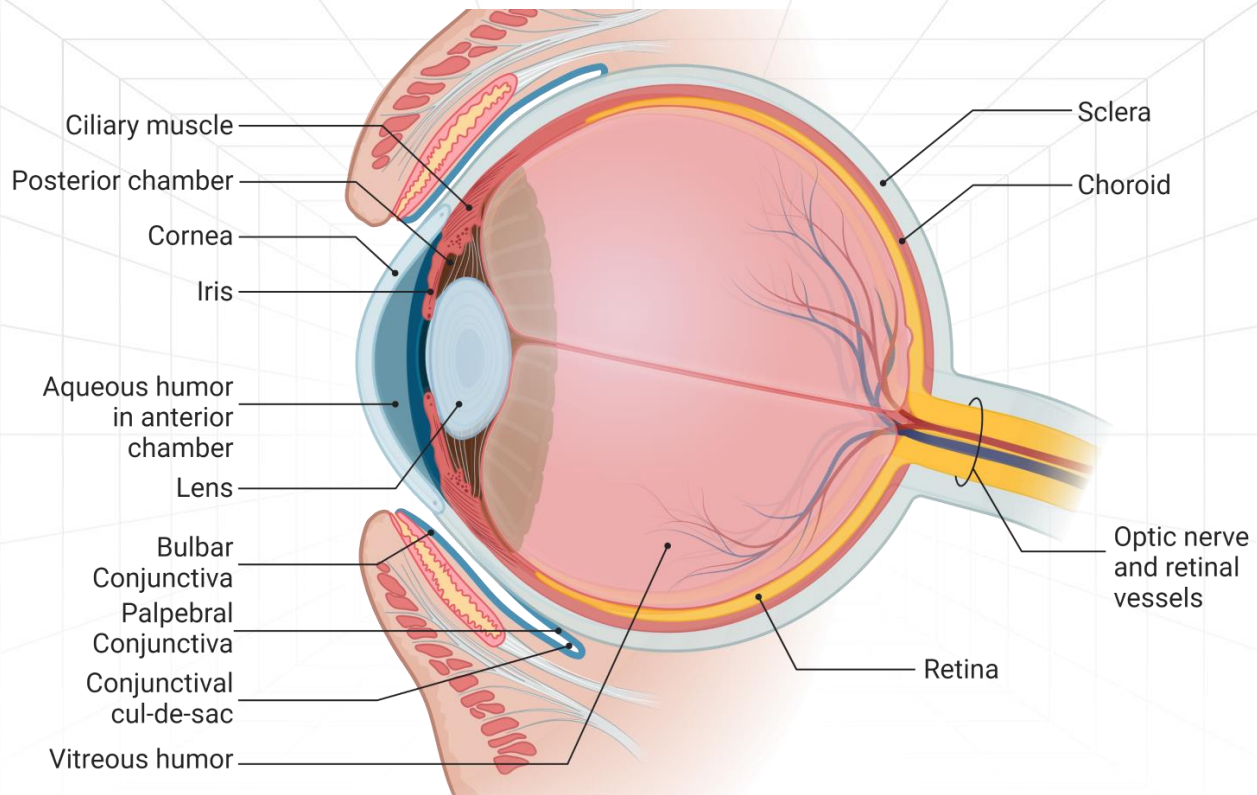
S+ *SimulationsPlus*

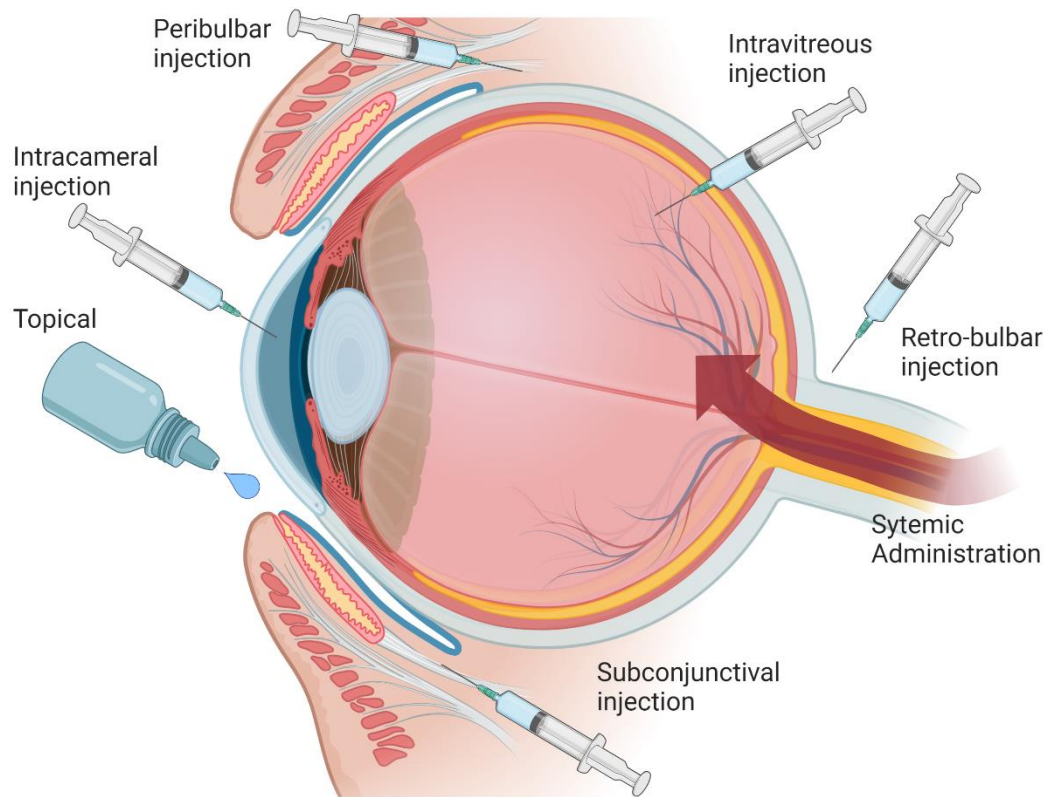
Cognigen | *DILIsym Services* | *Lixoft*

Ophthalmic drug products: leveraging M&S approaches to perform inter-species predictions and support drug product development and approval

Maxime Le Merdy
Senior Scientist

27-10-2022





*“Complex generics are products that have complex active ingredients, formulations, dosage forms, or **routes of administration**, or are complex drug-device combination products.”*

Ophthalmic Drug product Bioequivalence

Q3

Characterization and
Performance

Does not allow
Q1/Q2 differences

In Vitro only
option

Q3

Characterization and
Performance

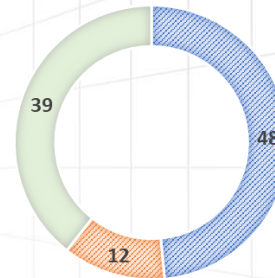
Does not allow
Q1/Q2 differences

In Vitro only
option



Option available for the
simplest formulation:

SOLUTION



... and some other drug
products (see PSGs)

Ophthalmic Drug product Bioequivalence

Clinical studies

Pk or PD endpoint

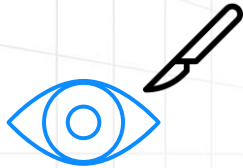
Allows Q1/Q2/Q3 differences

In Vivo

PK Endpoint Studies



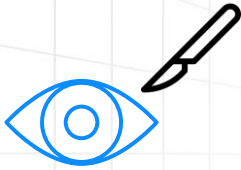
PK Endpoint Studies



Surgeries:

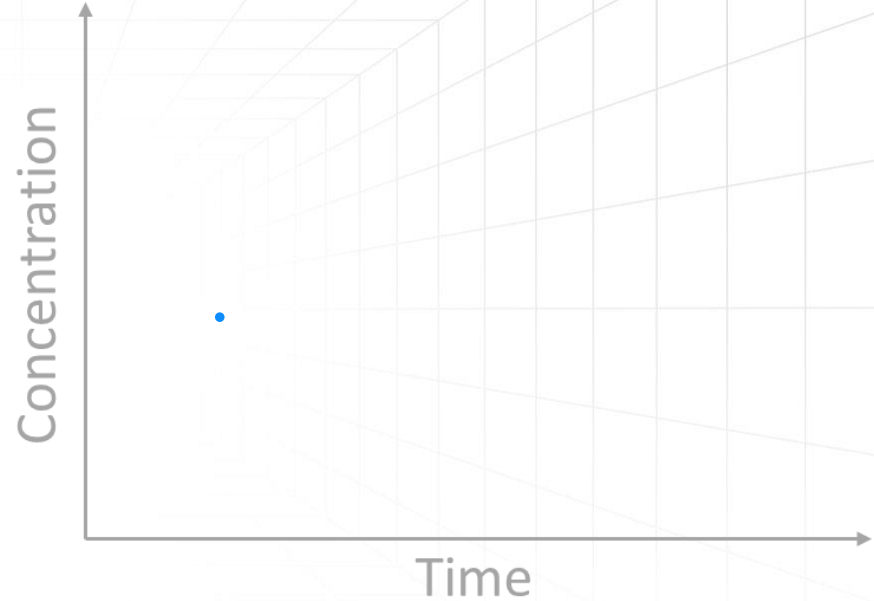
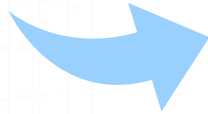
- Cataract
- Keratoplasty
- Vitrectomy

PK Endpoint Studies

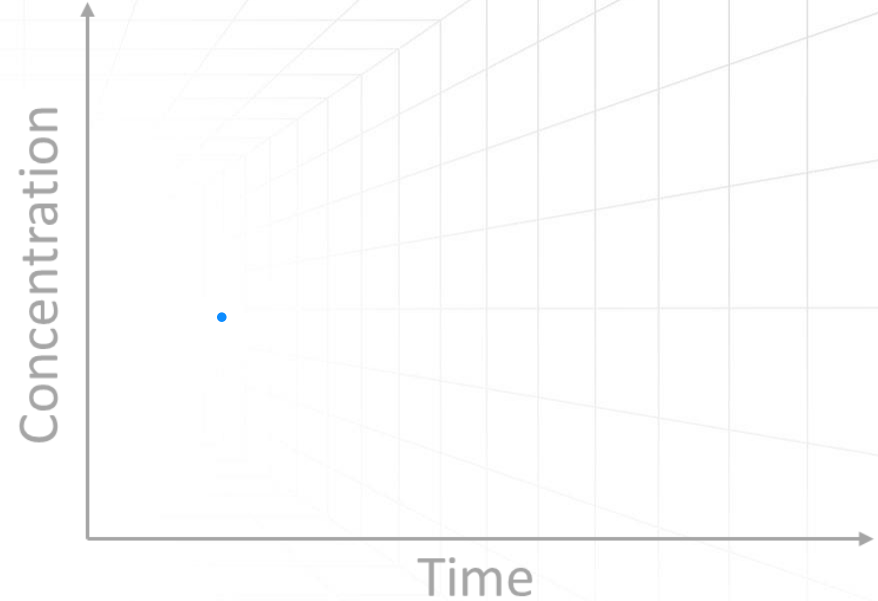


Surgeries:

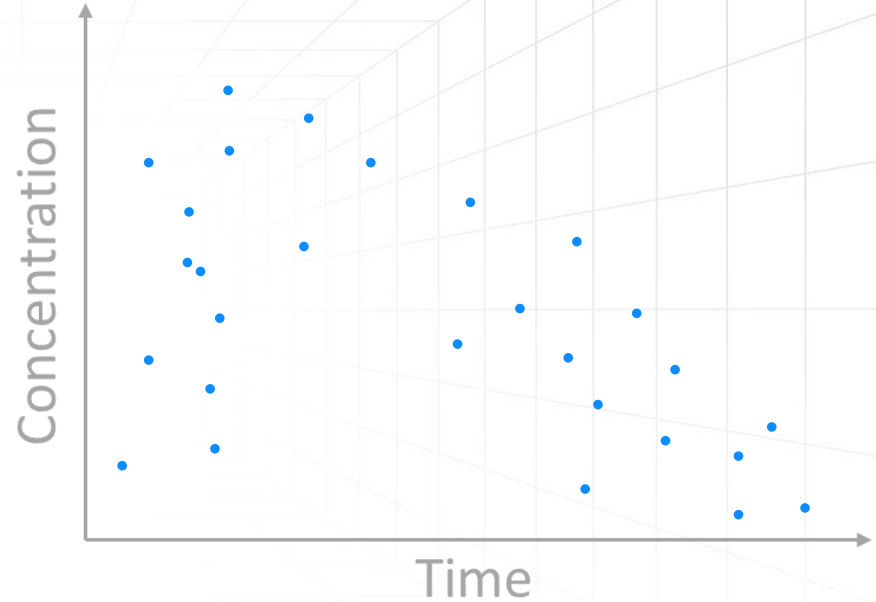
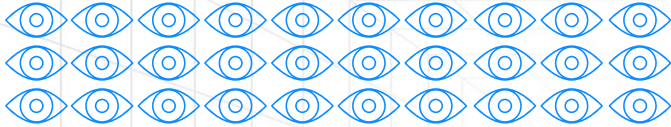
- Cataract
- Keratoplasty
- Vitrectomy



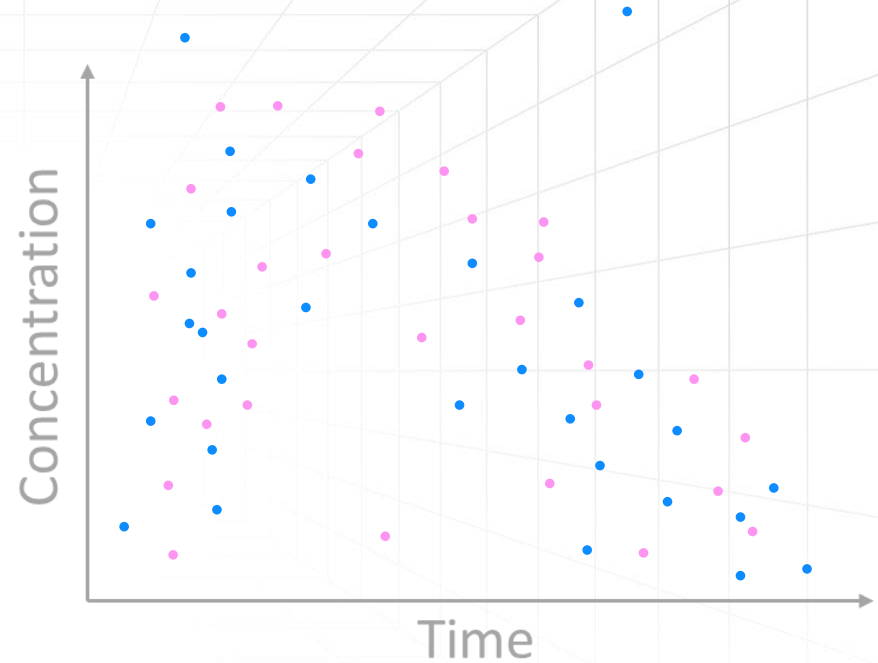
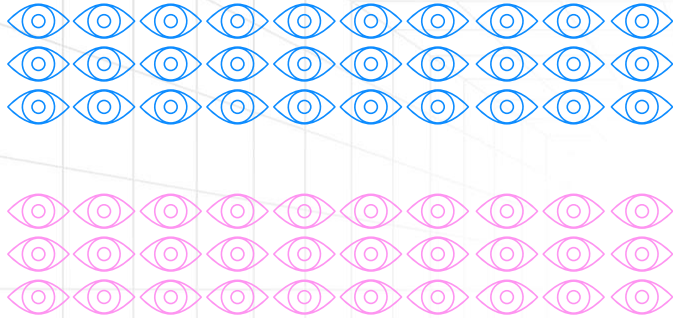
PK Endpoint Studies



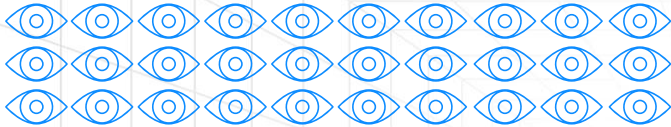
PK Endpoint Studies



PK Endpoint Studies

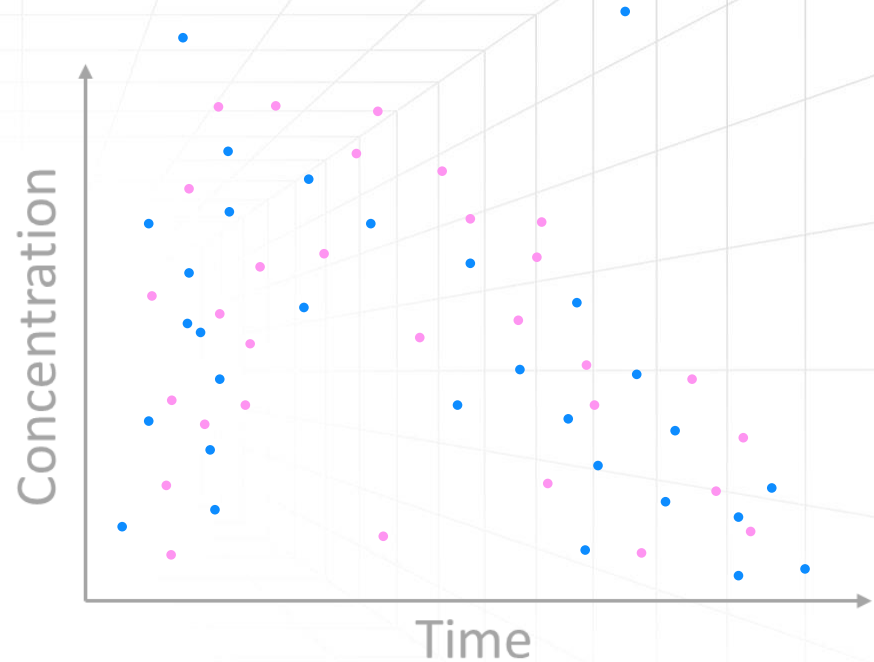


PK Endpoint Studies



BE calculation based on observed local concentrations:

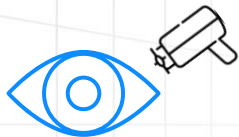
- *High variability*
- *One sample per patient*
 - *Parallel design*
- *Co-morbidities and co-treatments*
- *Cross-over design possible in some rare cases*



PD Endpoint Studies



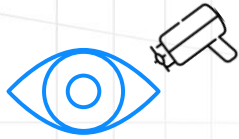
PD Endpoint Studies



PD measurements:

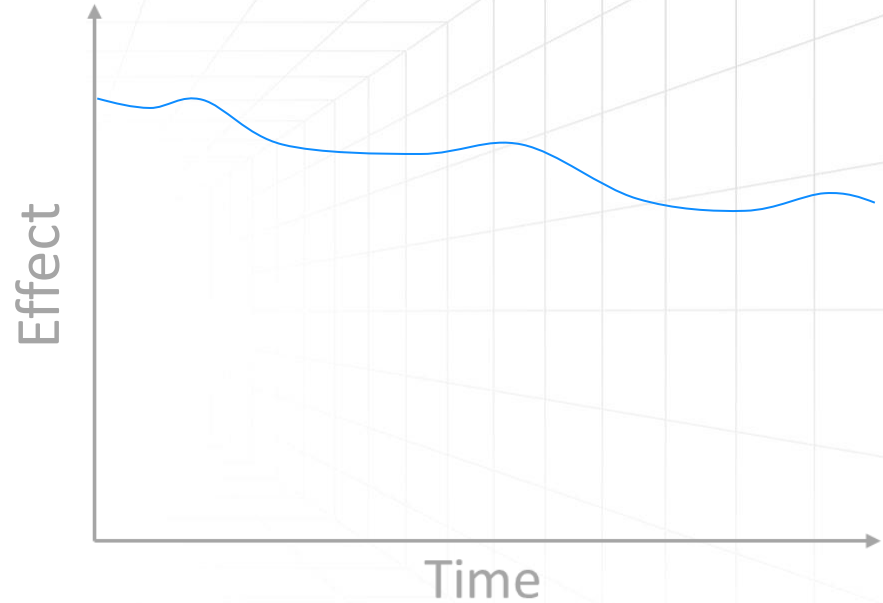
- IOP
- Inflammation
- Other (see PSGs)

PD Endpoint Studies

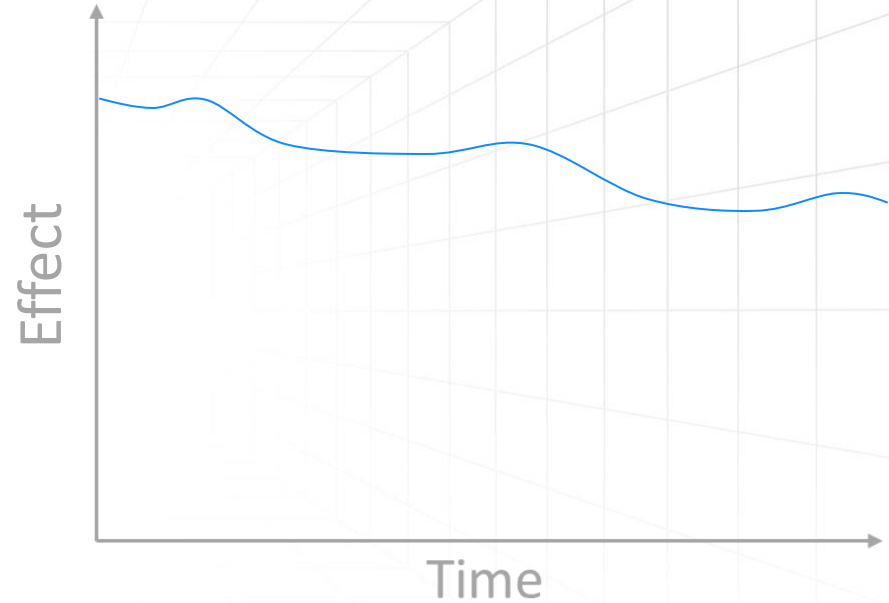


PD measurements:

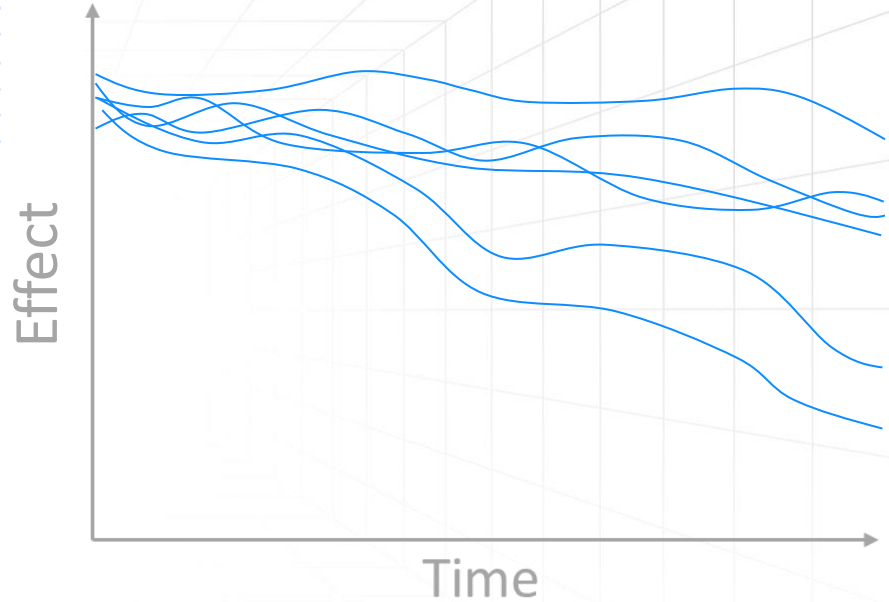
- IOP
- Inflammation
- Other (see PSGs)



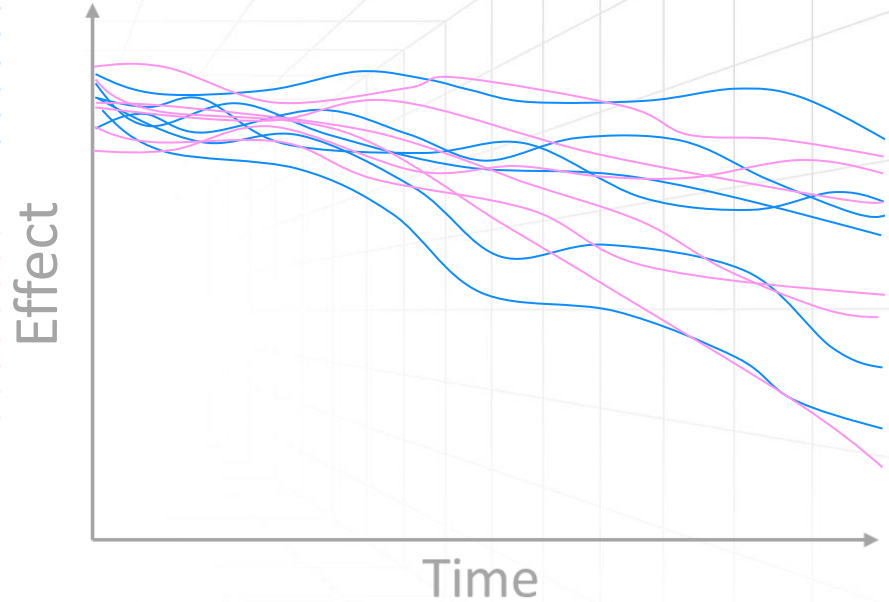
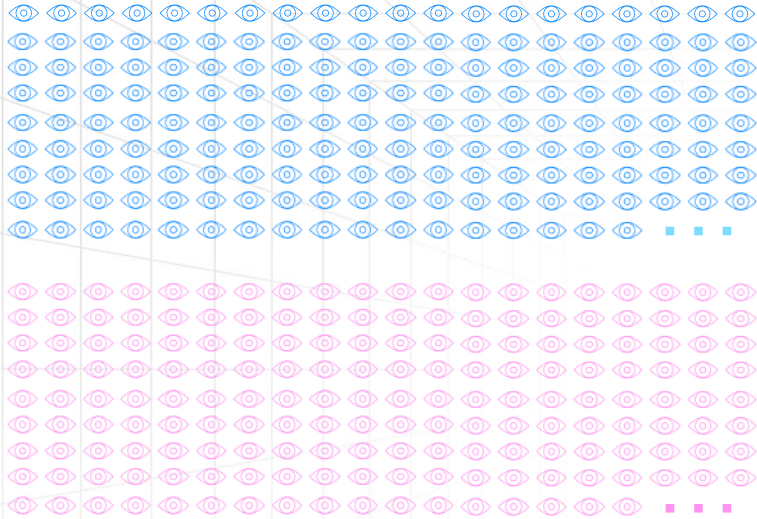
PD Endpoint Studies



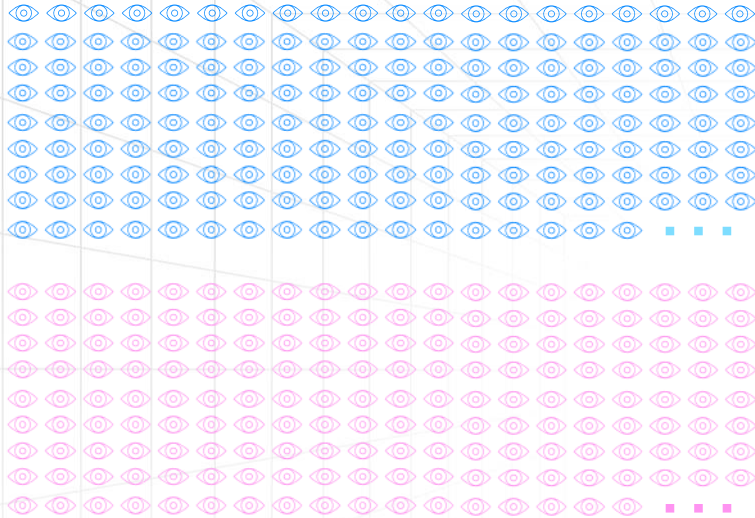
PD Endpoint Studies



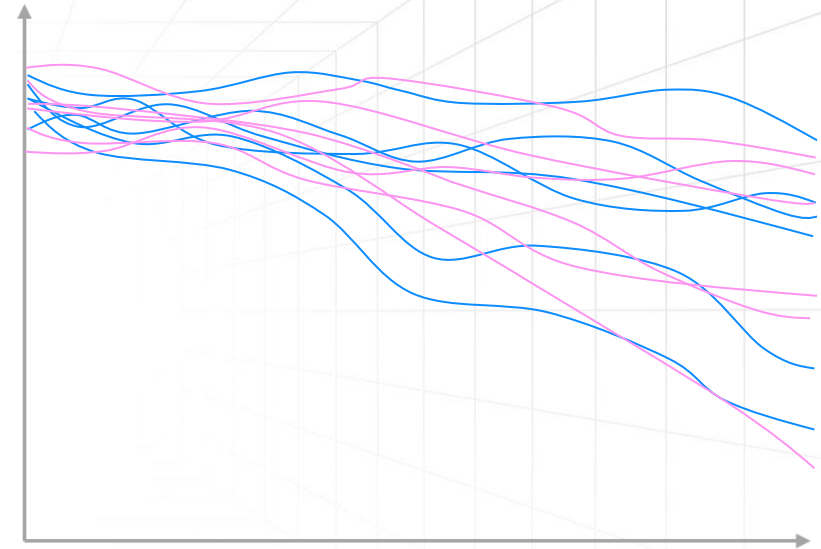
PD Endpoint Studies



PD Endpoint Studies



Effect



Time

BE calculation based on PD effect:

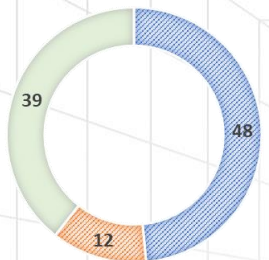
- *High variability*

“However, comparative clinical end-point BE studies are costly, and they can often be insensitive to formulation or dose differences when the drug exposure and clinical response relationship is flat.”

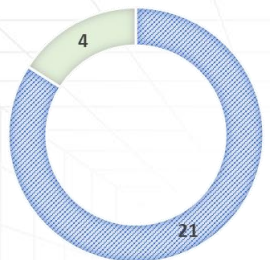
Zhao et al. 2019 CPT-PSP



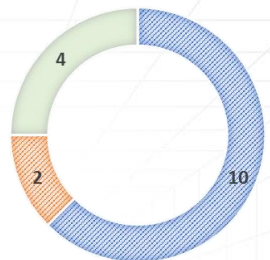
SOLUTION



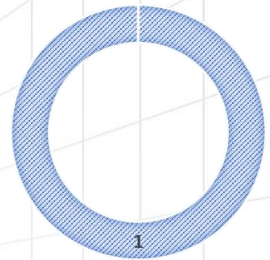
SUSPENSION



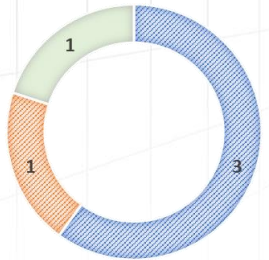
OINTMENT



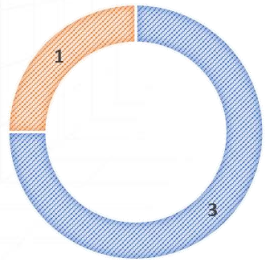
DRUG-ELUDING CONTACT LENS



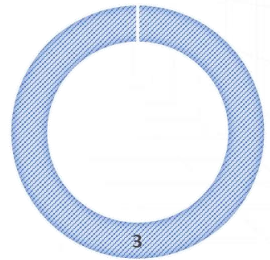
EMULSION





GEL




IMPLANT-INSERT



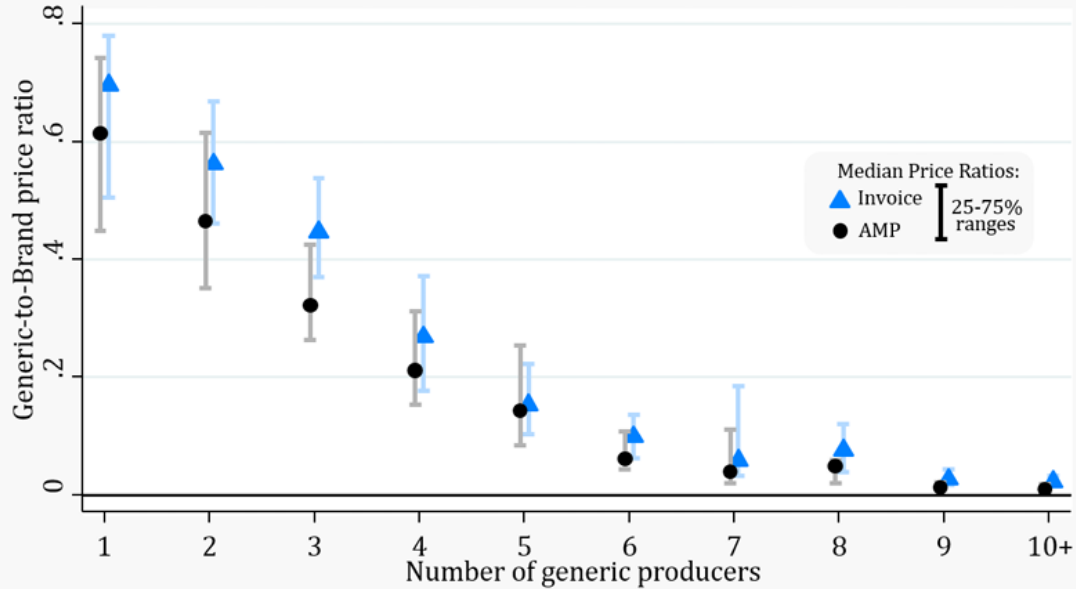
 = Number of RS without any generics on the US market

 = Number of RS with one generic on the US market

 = Number of RS with more than one generic on the US market

Generic Competition and Drug Prices

Median generic prices relative to brand price before generic entry



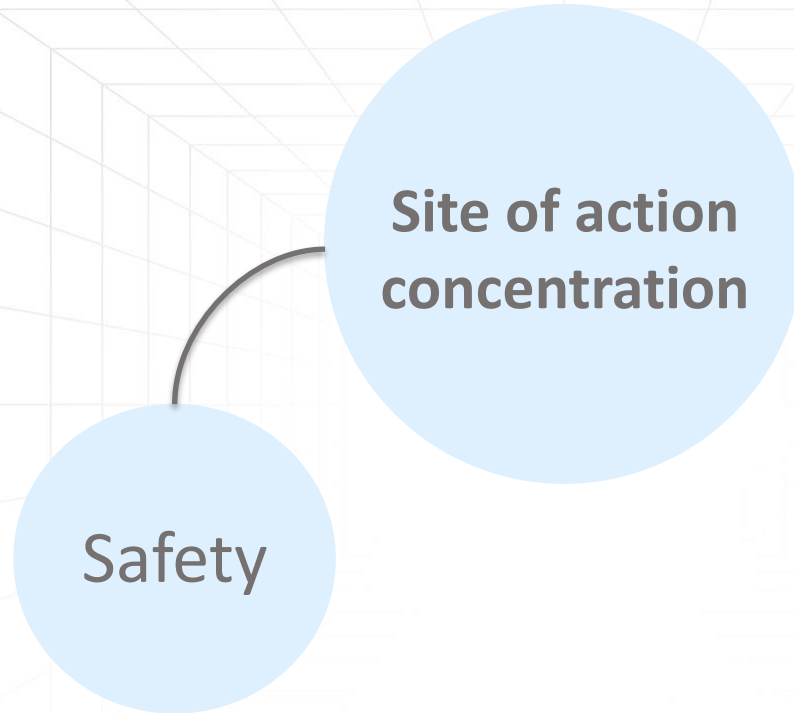
Generic drug products with initial generic entry from 2015-2017.

Based on IQVIA NSP invoice-based sales and units sold to pharmacies (▲) and average manufacturer prices (AMP) reported to CMS (●).

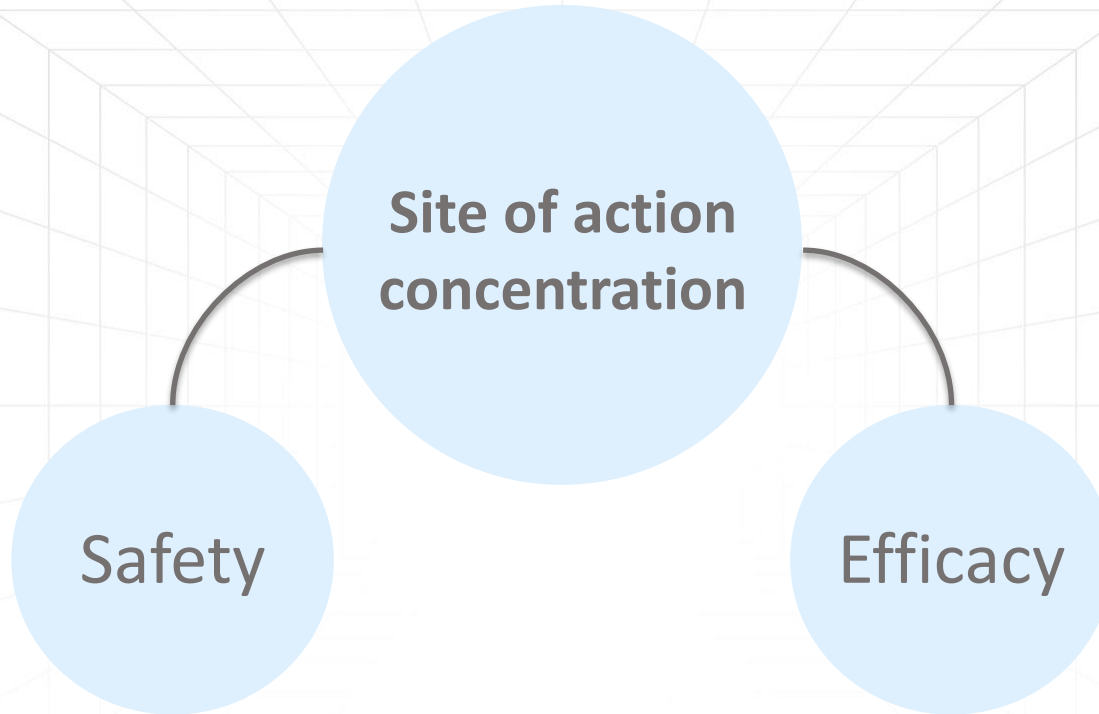
The issue

Site of action
concentration

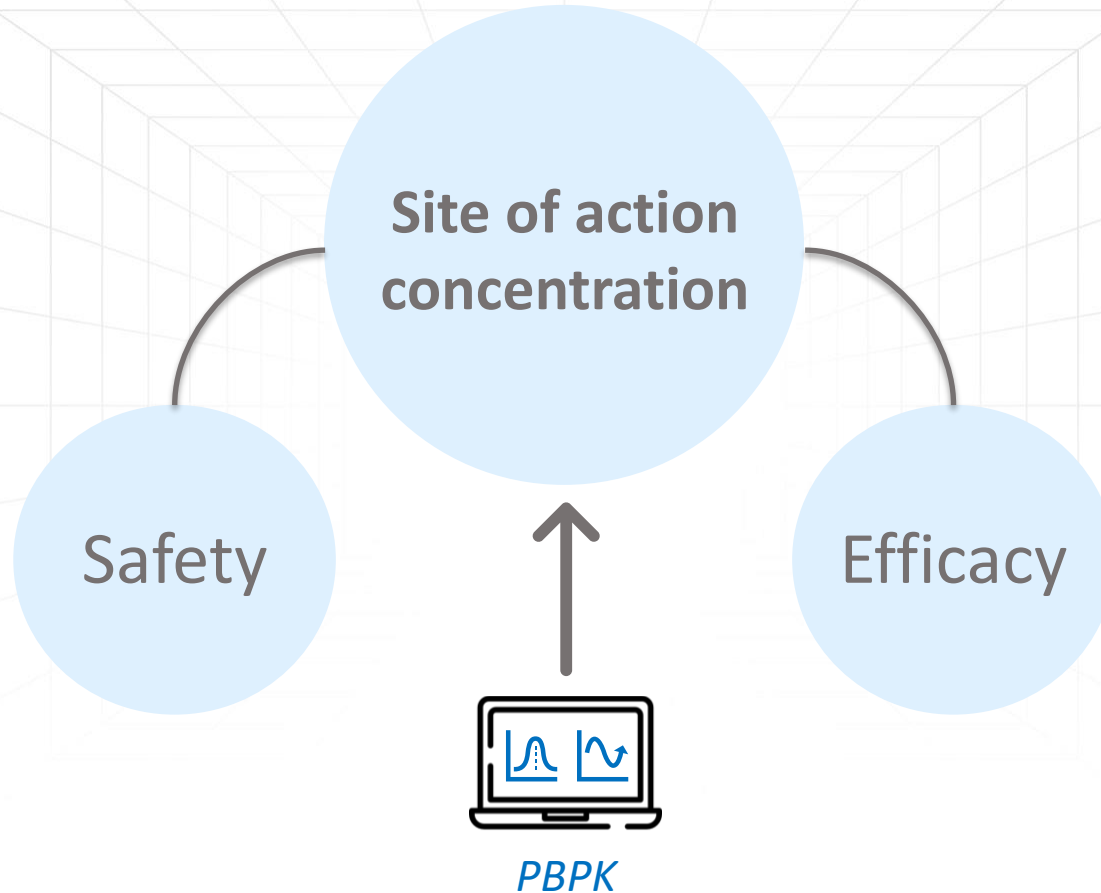
The issue

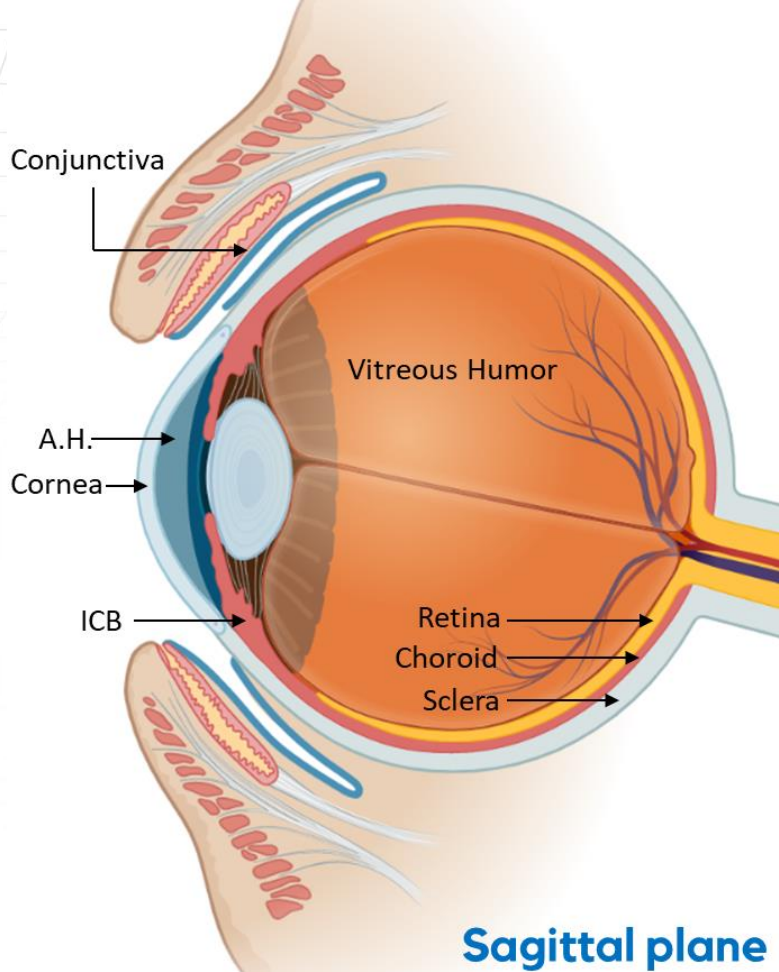
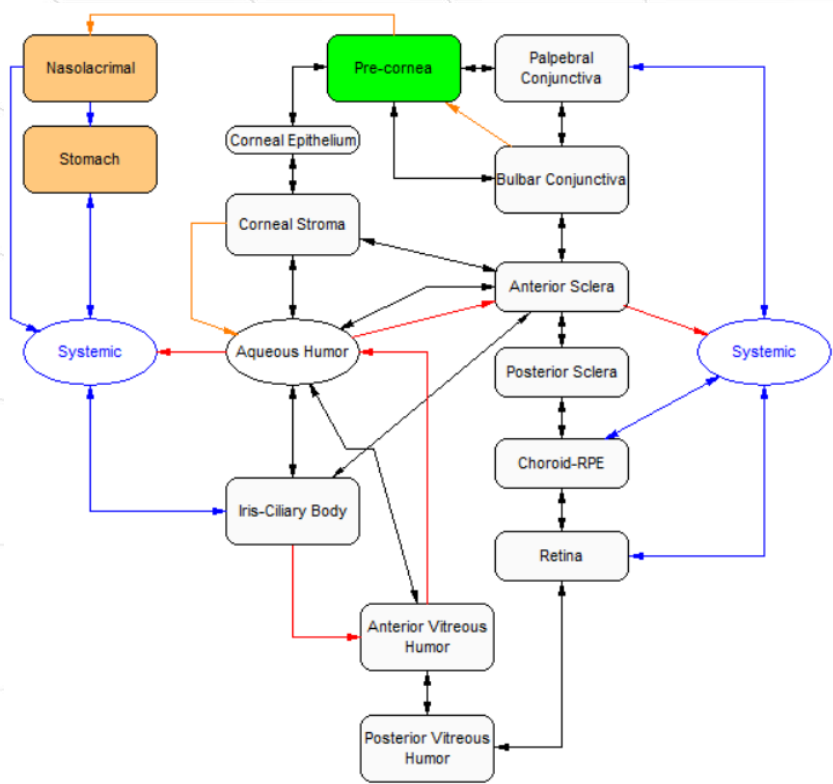


The issue



The issue





Sagittal plane



Aim:
Validate the OCAT model for ophthalmic ointments



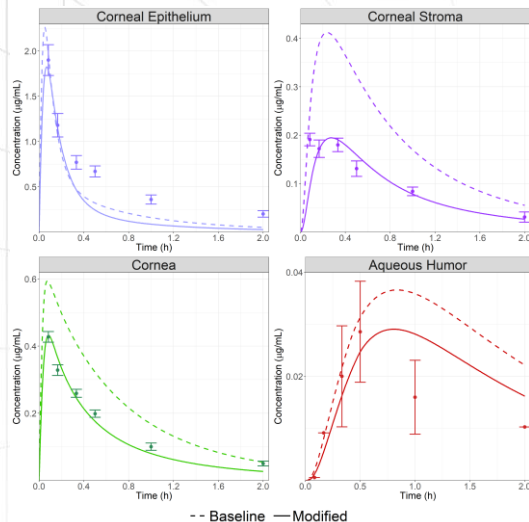
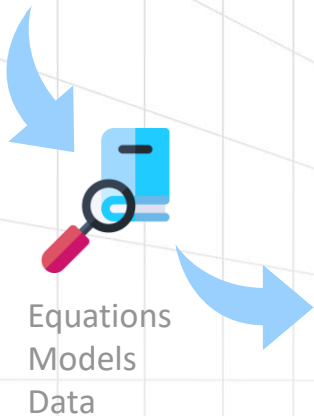
Aim:
Validate the OCAT model for ophthalmic ointments



Equations
Models
Data



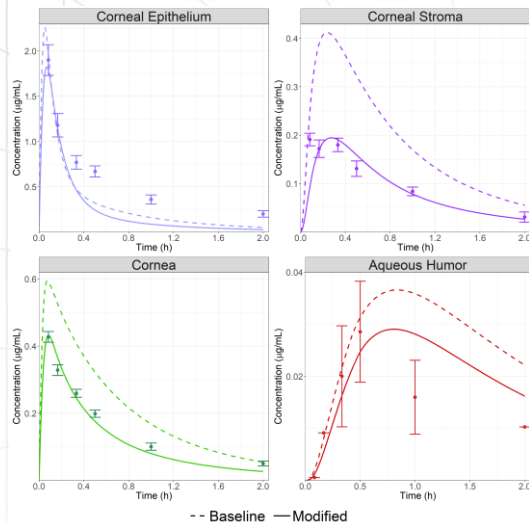
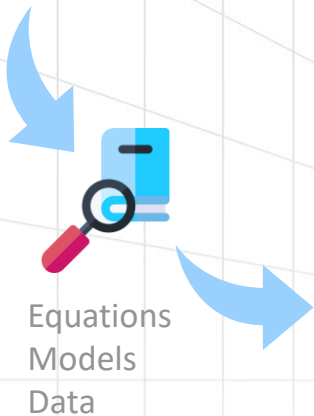
Aim:
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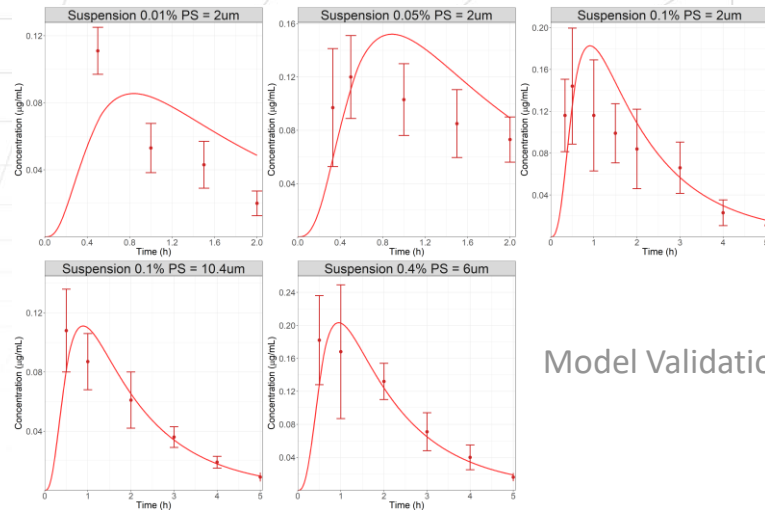
Model development for
validation compound
(Fluorometholone suspension)



Aim:
Validate the OCAT model for ophthalmic ointments



Model development for
validation compound
(Fluorometholone suspension)



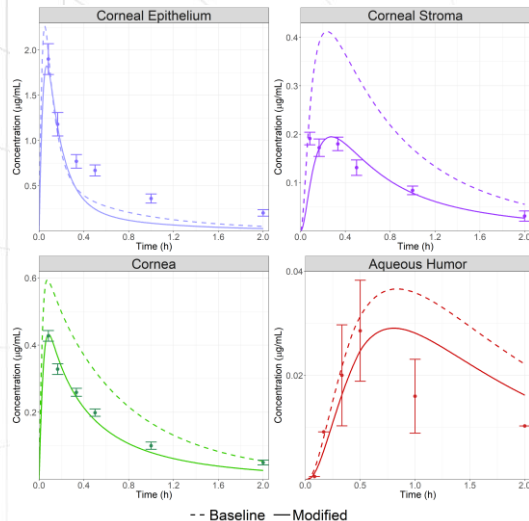
Model Validation



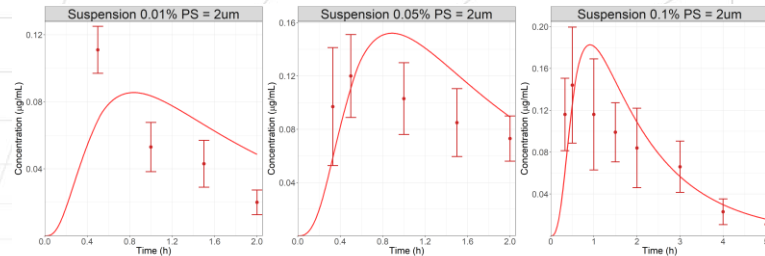
Aim:
Validate the OCAT model for ophthalmic ointments



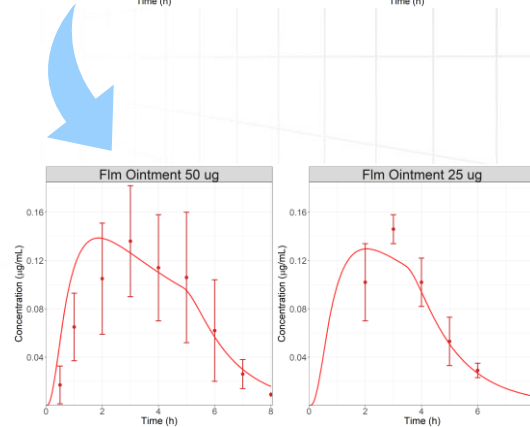
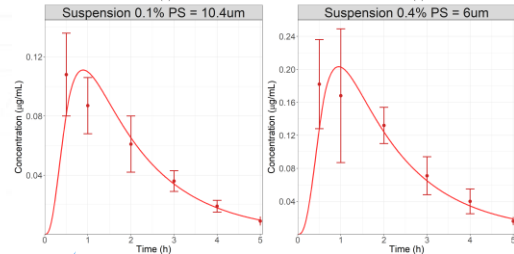
Equations
Models
Data



Model development for validation compound (Fluorometholone suspension)



Model Validation



Model Validation:
Fluorometholone Ointment

Application of Mechanistic Ocular Absorption Modeling and Simulation to Understand the Impact of Formulation Properties on Ophthalmic Bioavailability in Rabbits: a Case Study Using Dexamethasone Suspension

Maxime Le Merdy,¹
Eleftheria Tsakalozou,
Suresh Narayanasam,
Lei Zhang,⁵ Robert [unclear]

Physiologically Based Pharmacokinetic Model to Support Ophthalmic Suspension Product Development

Maxime Le Merdy, Ocular Physiologically Based Pharmacokinetic Modeling for Ointment Formulations

Maxime Le Merdy¹  • Jessica Spires¹ • Viera Lukacova¹ • Ming-Liang Tan² • Andrew Babiskin² • Xiaoming Xu³ • Liang Zhao² • Michael B. Bolger¹

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- How can PBPK modeling be used to **accelerate** the development of ophthalmic generic drugs?
- What can we **learn** using PBPK model?

➔ What can we **do** using PBPK model?



GastroPlus[®]

Simulations Plus Receives New Grant Award from the FDA

Novel PBPK/PD modeling strategies for ophthalmic drug products will inform regulatory decision-making

 **SimulationsPlus**

SCIENCE + SOFTWARE = SUCCESS

Pharmaceutical Research

<https://doi.org/10.1007/s11095-022-03390-z>

ORIGINAL RESEARCH ARTICLE

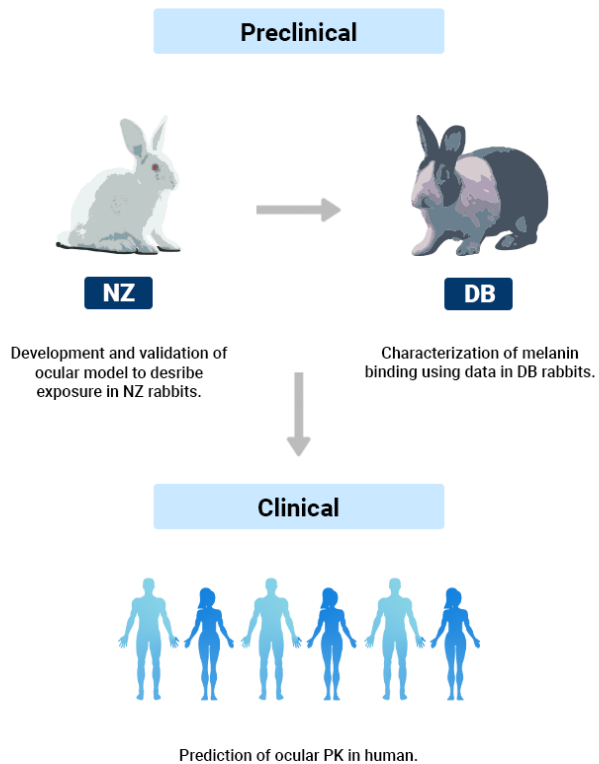
Clinical Ocular Exposure Extrapolation for Ophthalmic Solutions Using PBPK Modeling and Simulation

Maxime Le Merdy¹  · Farah AlQaraghuli¹ · Ming-Liang Tan² · Ross Walenga² · Andrew Babiskin² · Liang Zhao² · Viera Lukacova¹

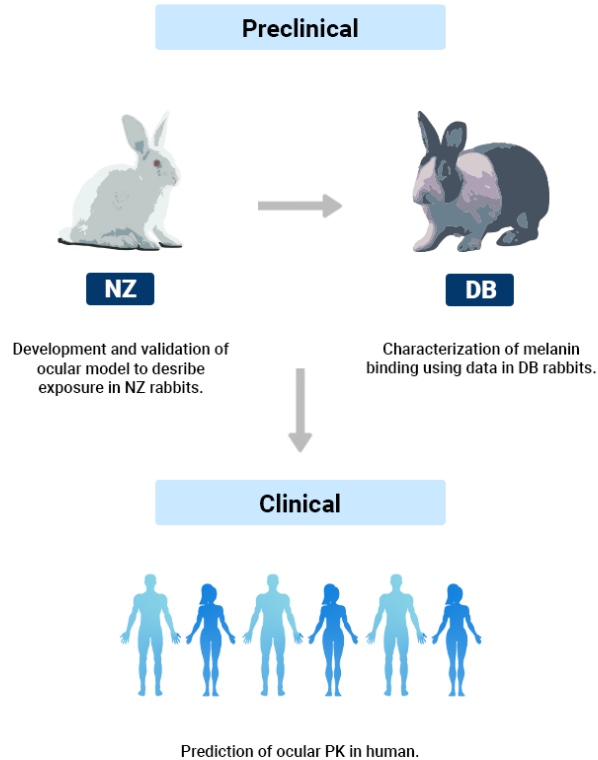
Received: 16 June 2022 / Accepted: 5 September 2022

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Validation of preclinical to clinical extrapolation using the OCAT™ model



Validation of preclinical to clinical extrapolation using the OCAT™ model



Initial focus on ophthalmic solutions:
→ simplest dosage form

PK extrapolation only

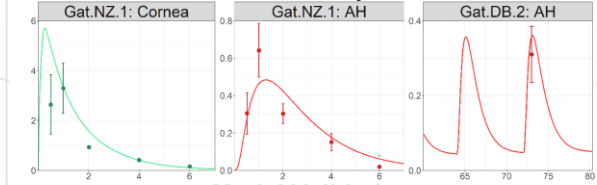
Three case studies (published):

- levofloxacin
- moxifloxacin
- gatifloxacin

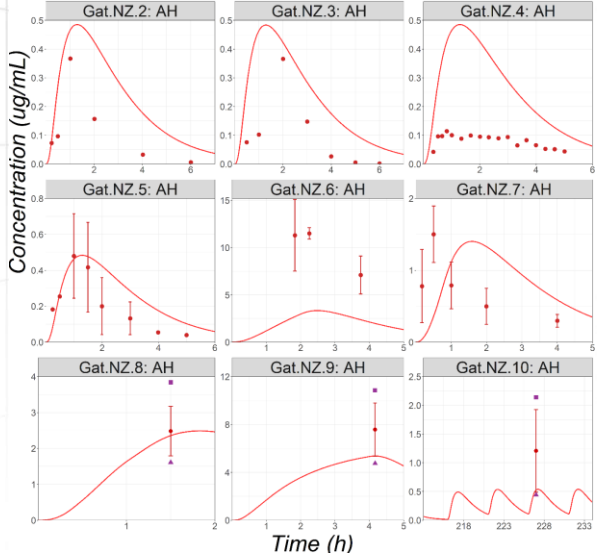
Gatifloxacin



Model Development



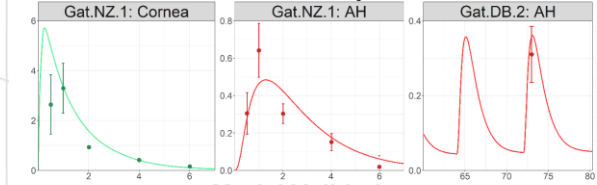
Model Validation



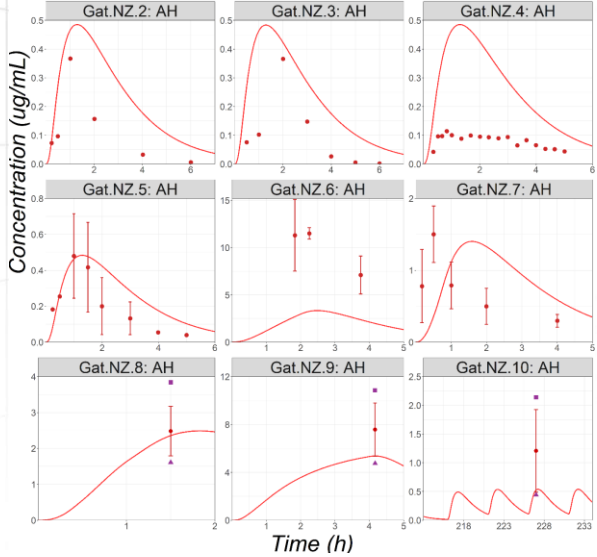
Gatifloxacin



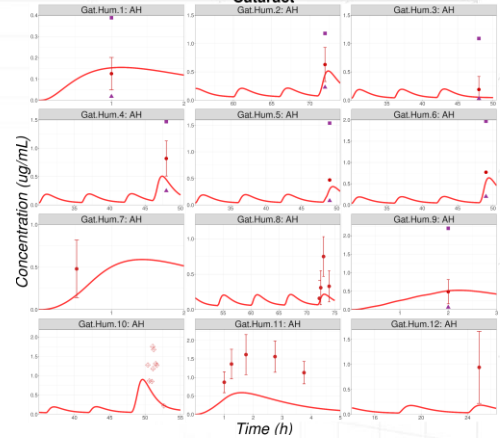
Model Development



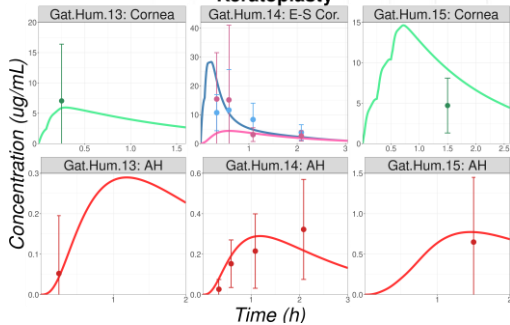
Model Validation



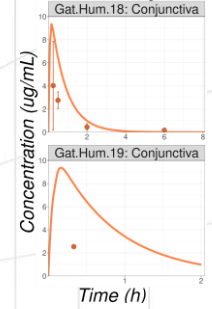
Cataract



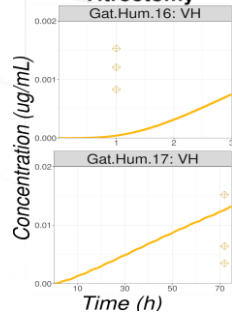
Keratoplasty

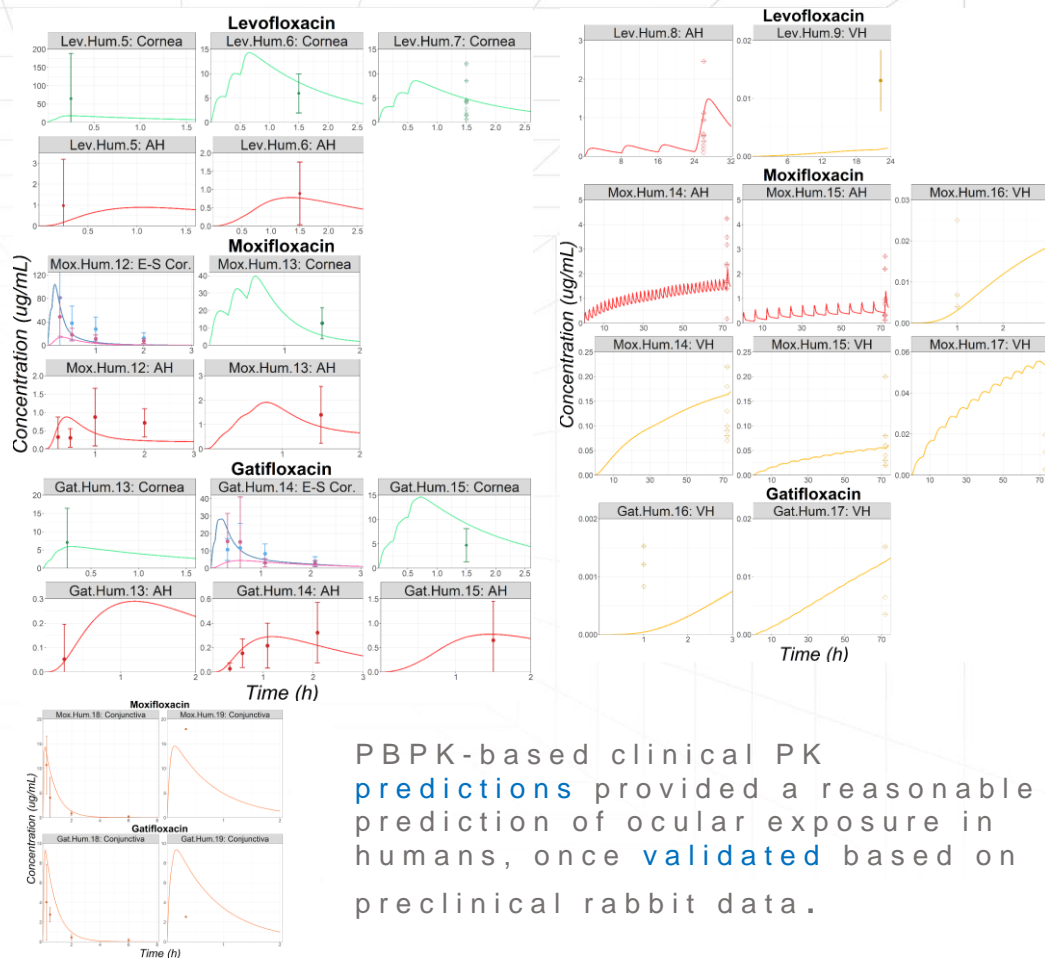
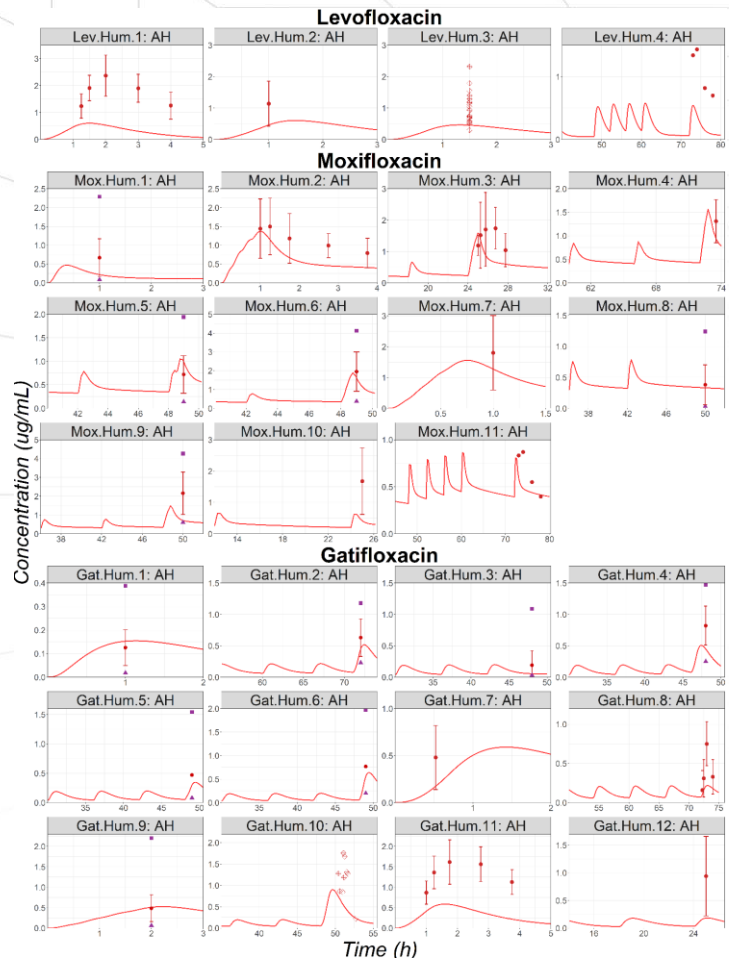


Healthy



Vitrectomy





PBPK-based clinical PK predictions provided a reasonable prediction of ocular exposure in humans, once validated based on preclinical rabbit data.

Conclusions

- BE evaluation of ophthalmic drug products is a challenge limiting access to affordable drugs for the US patients
- PK and PD clinical studies present significant limitations for generics developments
- Ocular PBPK models present an interesting approach to support the regulatory assessment of complex generic drug products
- The OCAT model demonstrated its ability to predict the clinical PK for ophthalmic solutions once validated based on rabbit data
- Additional research is ongoing for other, more complex, dosage forms.

Acknowledgment

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Farah AlQaraghuli
Dr. Viera Lukacova

FDA:

Dr. Ming-Liang Tan
Dr. Ross Walenga
Dr. Andrew Babiskin
Dr. Liang Zhao





Thank you!