Ophthalmic clinical PK/PD prediction using PBPK model validated against preclinical datasets

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Senior Scientist

Please note: this presentation, including questions from the audience, is being recorded and may be made available.

89%

Prescription dispended

27%

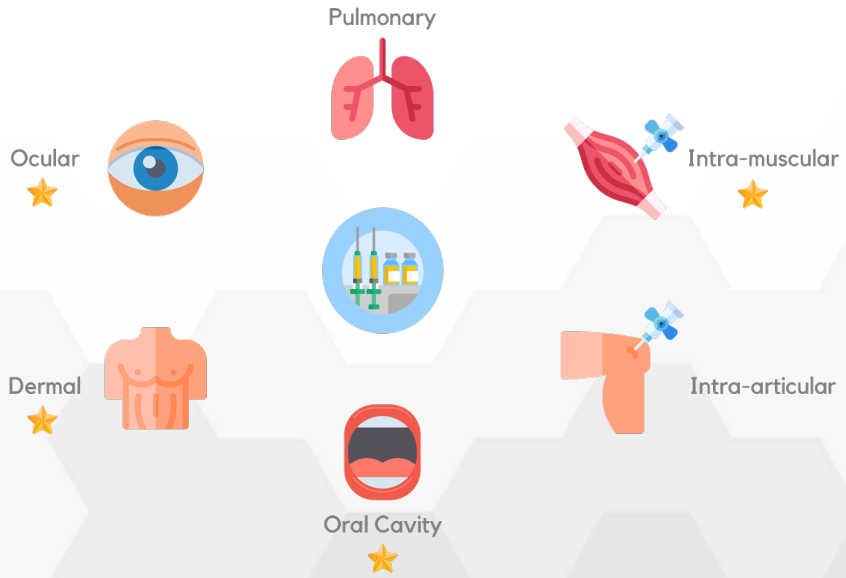
Medicine spending

One of FDA's **mission** is to **promote** generic drug products development

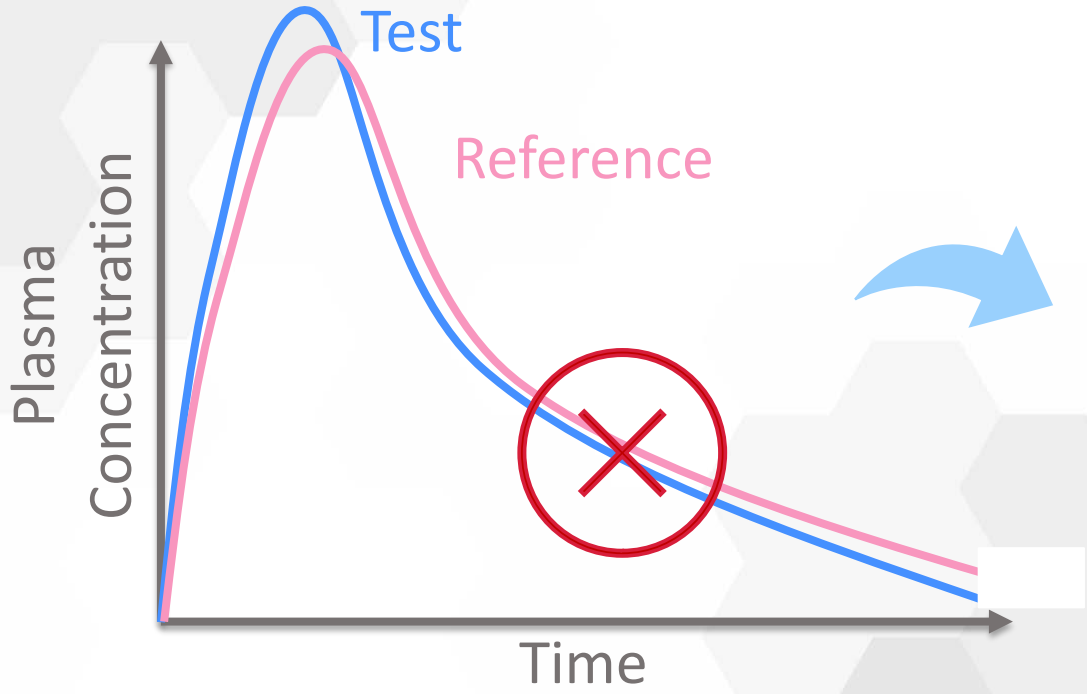
Specific **issues** for locally acting drug (LAD)

LAD

- Local site of action is local: skin, lungs, eyes, the gastrointestinal tract…
- Drug products not intended to be absorbed into the bloodstream
- If the API is detectable in plasma, does the plasma concentration time course reflect local concentrations?



Bioequivalence



90% confidence interval of the ratio of a log-transformed exposure measure (AUC and/or C_{max}) falls completely within the range 80-125%

LAD Bioequivalence

Q3

Characterization and Performance

Does not allow Q1/Q2 differences

In Vitro only option

Clinical studies

Pk or PD endpoint

Allows Q1/Q2/Q3 differences

In Vivo

LAD Bioequivalence

Q1

Same components

Q2

Same concentrations

Q3

Same matter arrangement

LAD Bioequivalence

Q1

Same components

excipients

Q2

Same concentrations

% excipients

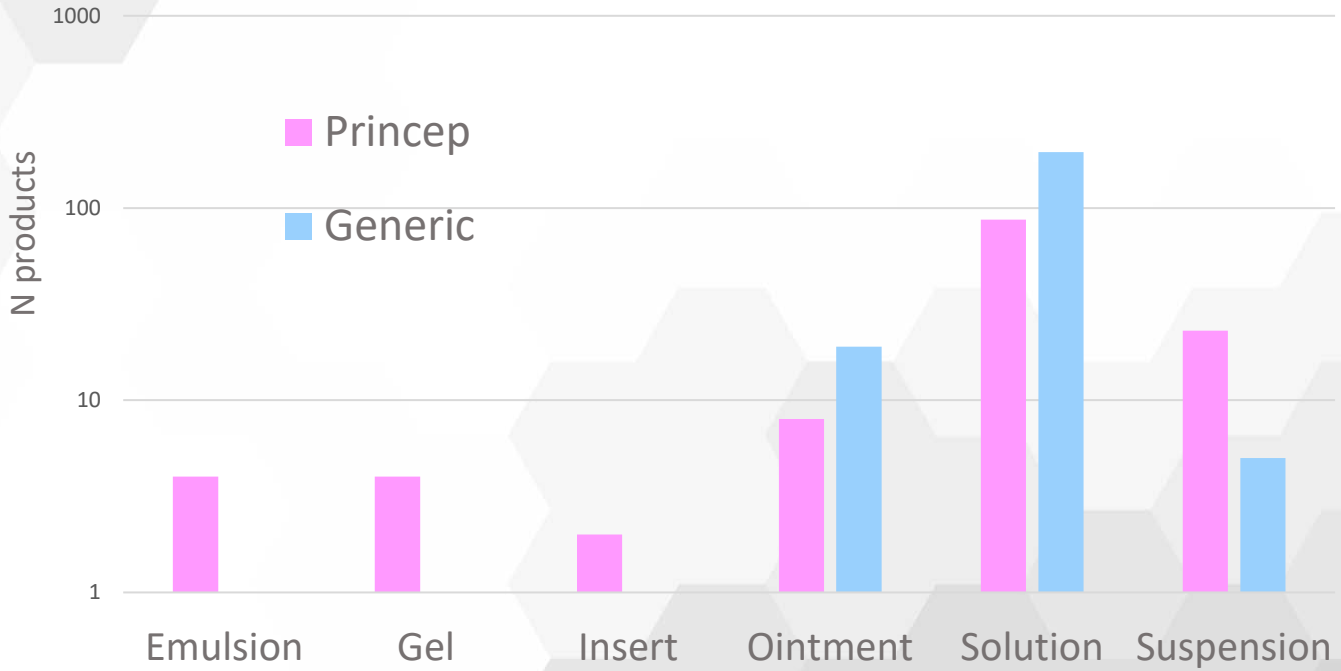
Q3

Same matter arrangement

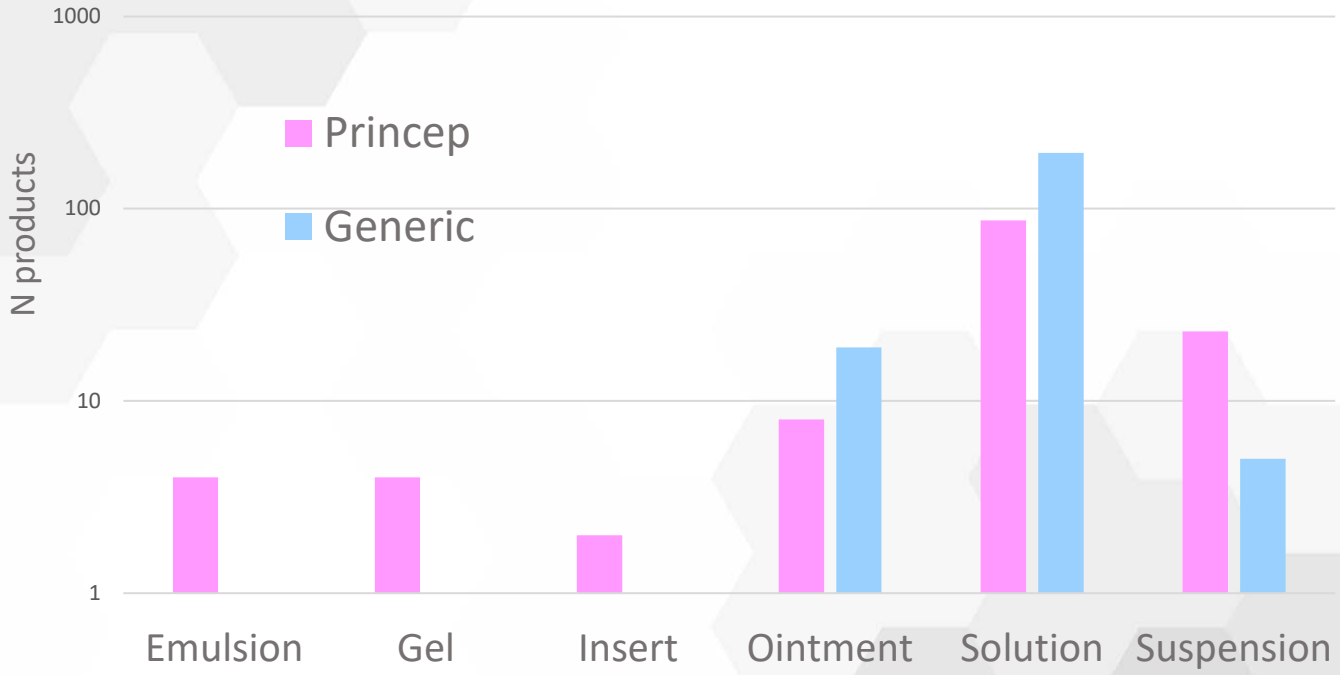
5% rule

LAD Bioequivalence

Ophthalmic drugs on the US. Market



Ophthalmic drugs on the US. Market



Q1

Same components

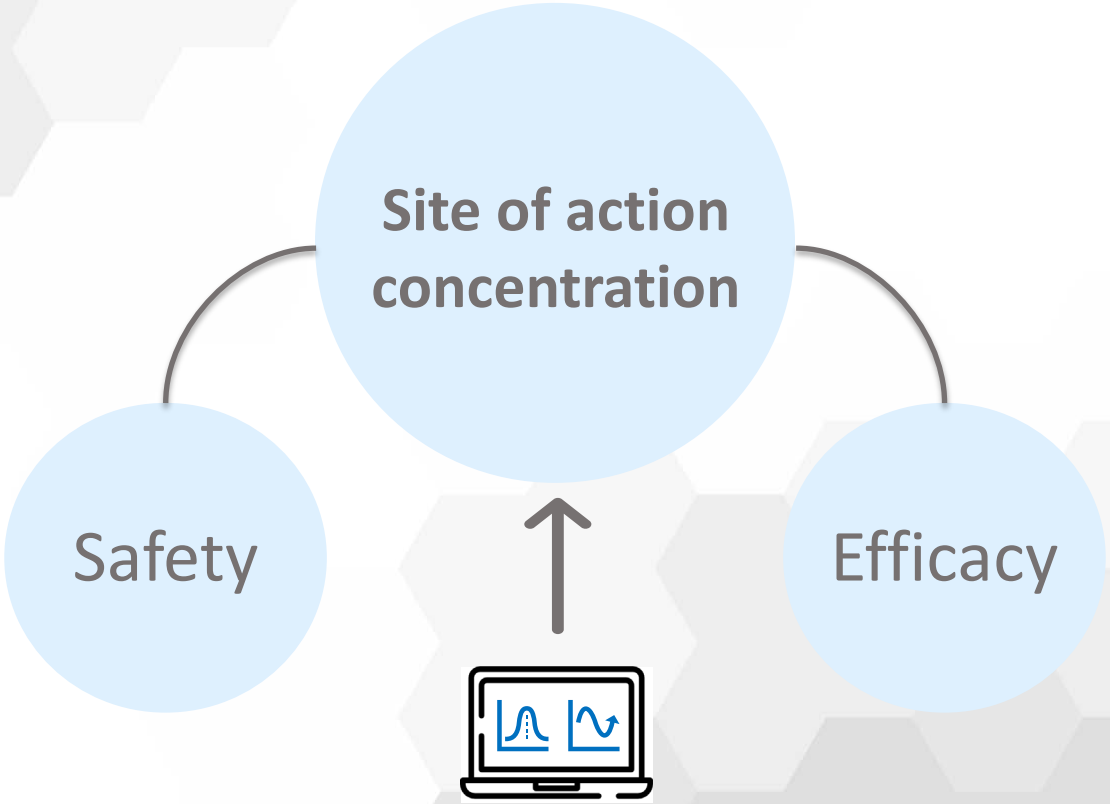
Q2

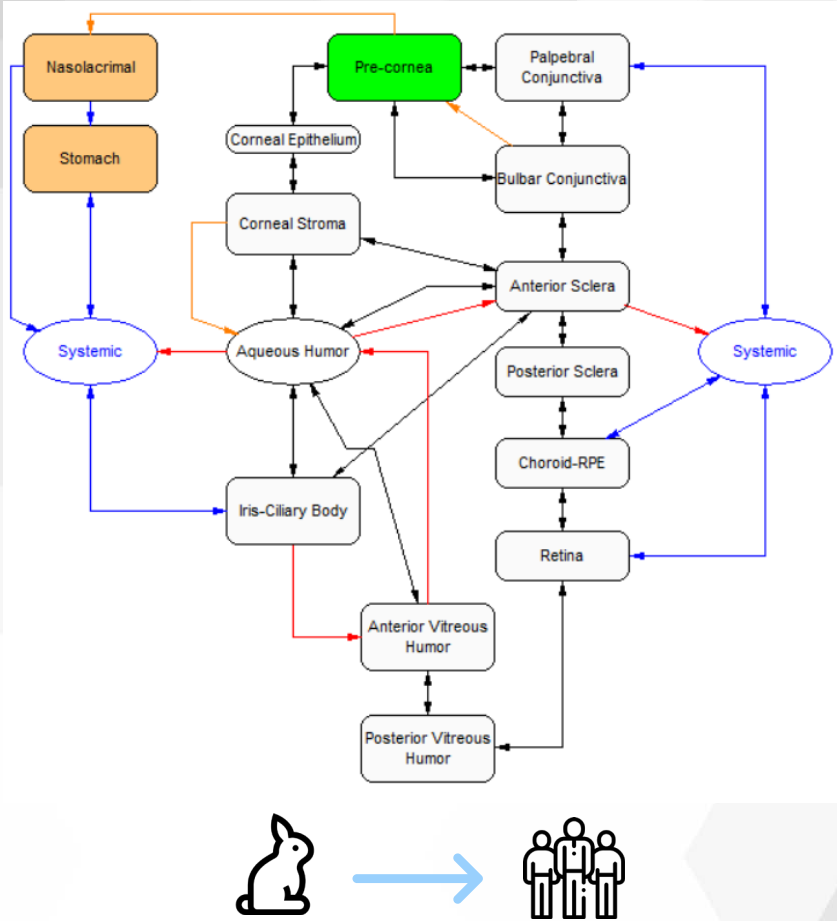
Same concentrations

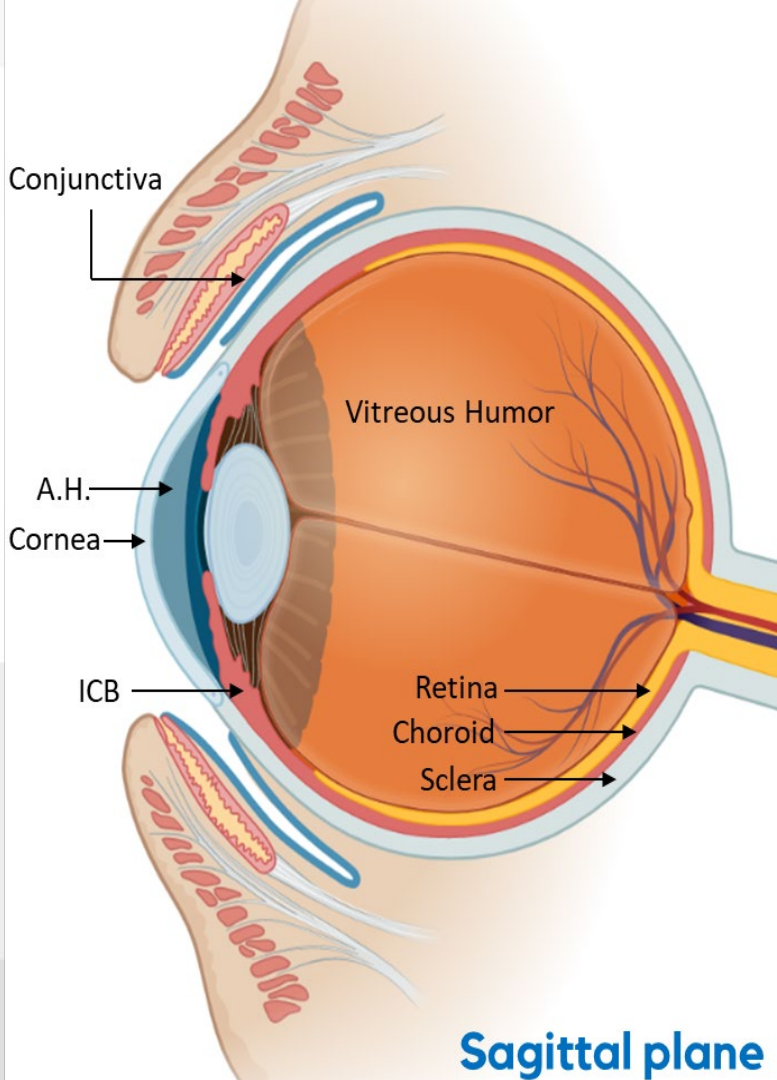
Q3

Same matter arrangement

The issue







Sagittal plane

Creation of first ocular PBPK

First FDA grant

Second FDA grant

2010

2014

2017

2020

2023

V1

V2

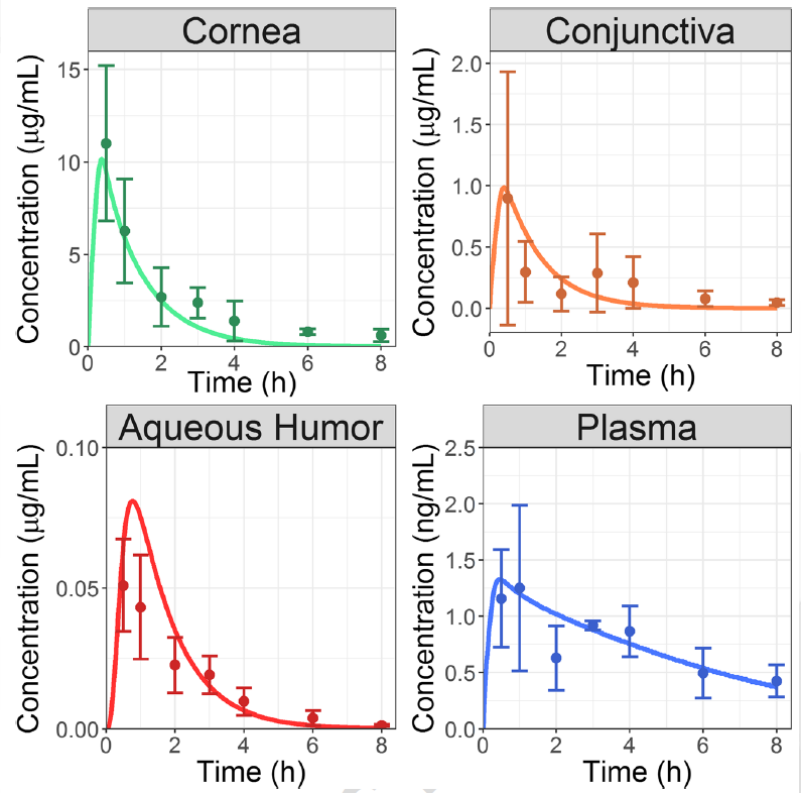
V3

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

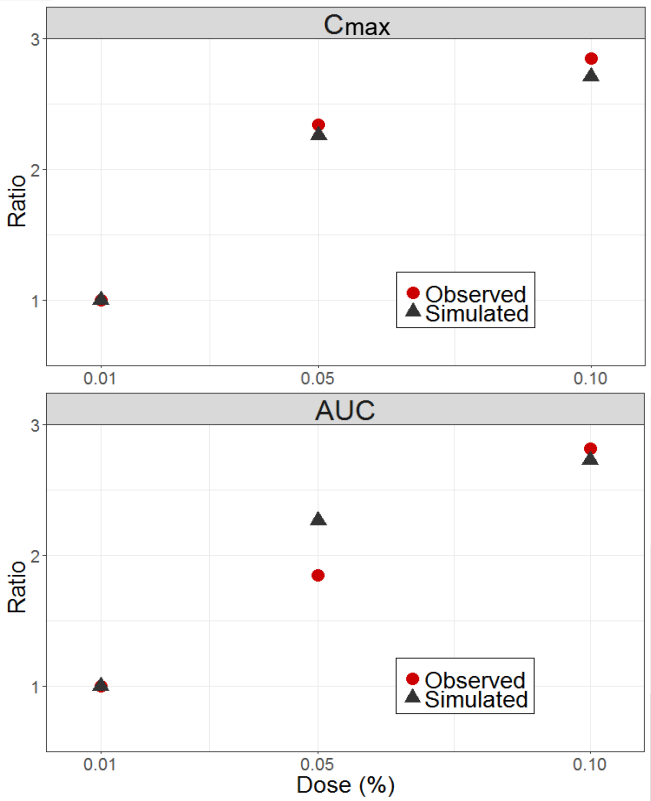
Maxime Le Merdy,[1] Jianghong Fan,[1,6] Michael B. Bolger,[2] Viera Lukacova,[2] Jessica Spires,[2] Eleftheria Tsakalozou,[1] Vikram Patel,[3] Lin Xu,[3] Sharron Stewart,[3] Ashok Chockalingam,[3] Suresh Narayanasamy,[3] Rodney Rouse,[3] Murali Matta,[3] Andrew Babiskin,[1] Darby Kozak,[4] Stephanie Choi,[5] Lei Zhang,[5] Robert Lionberger,[5] and Liang Zhao[1]

How can PBPK modeling be used to accelerate the development of ophthalmic generic drugs?

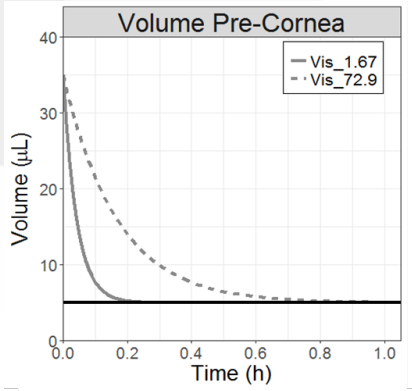
Model development



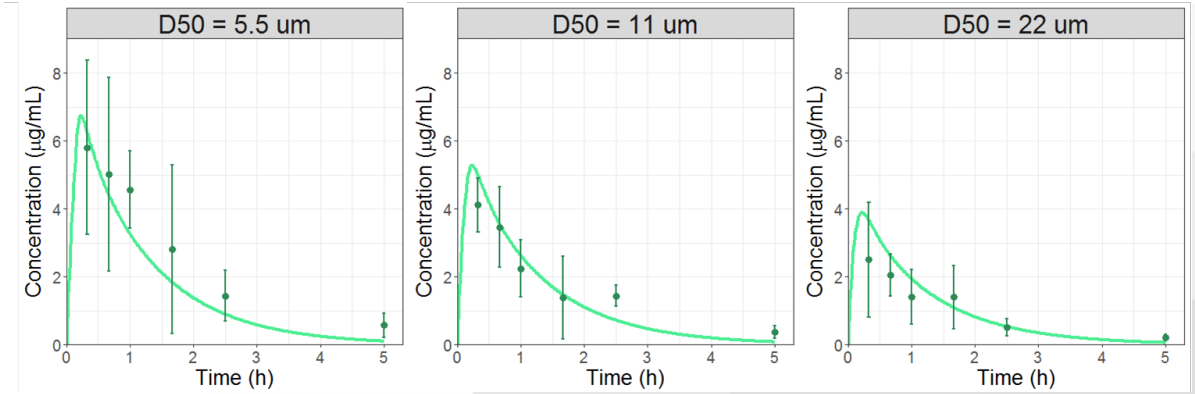
Model Validation



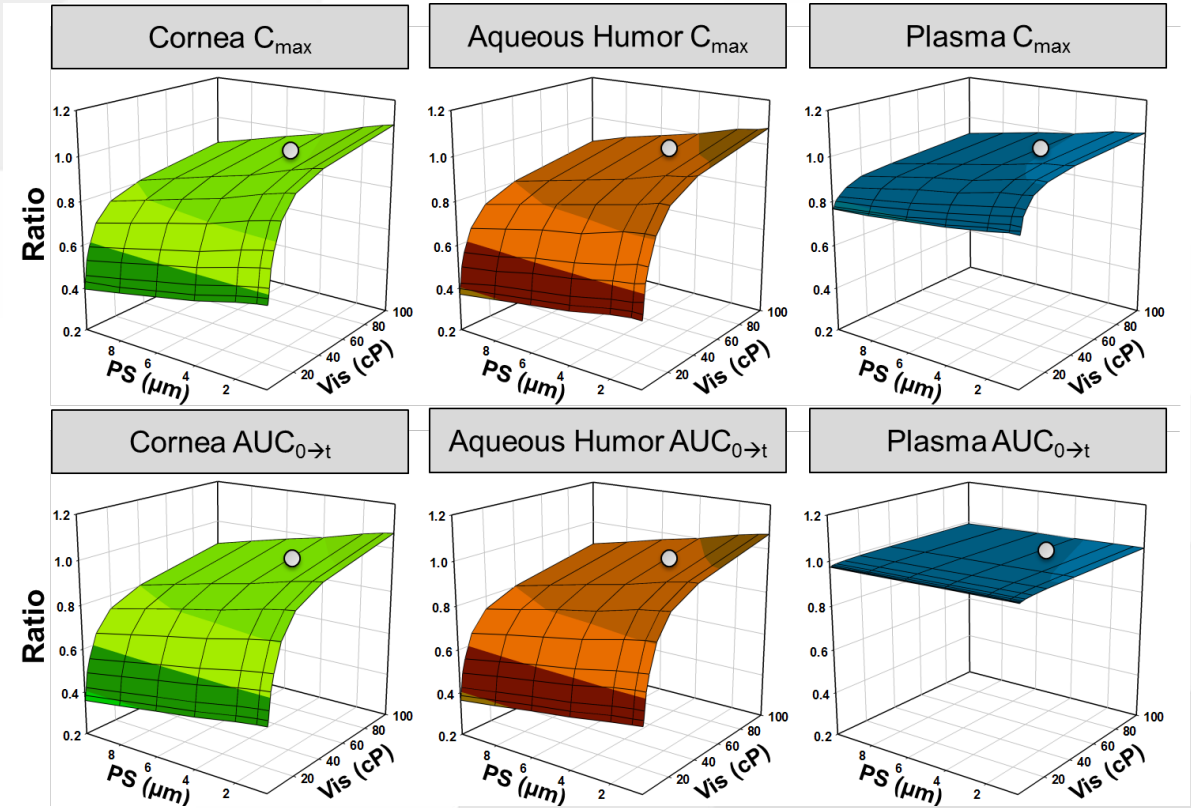
Model Validation



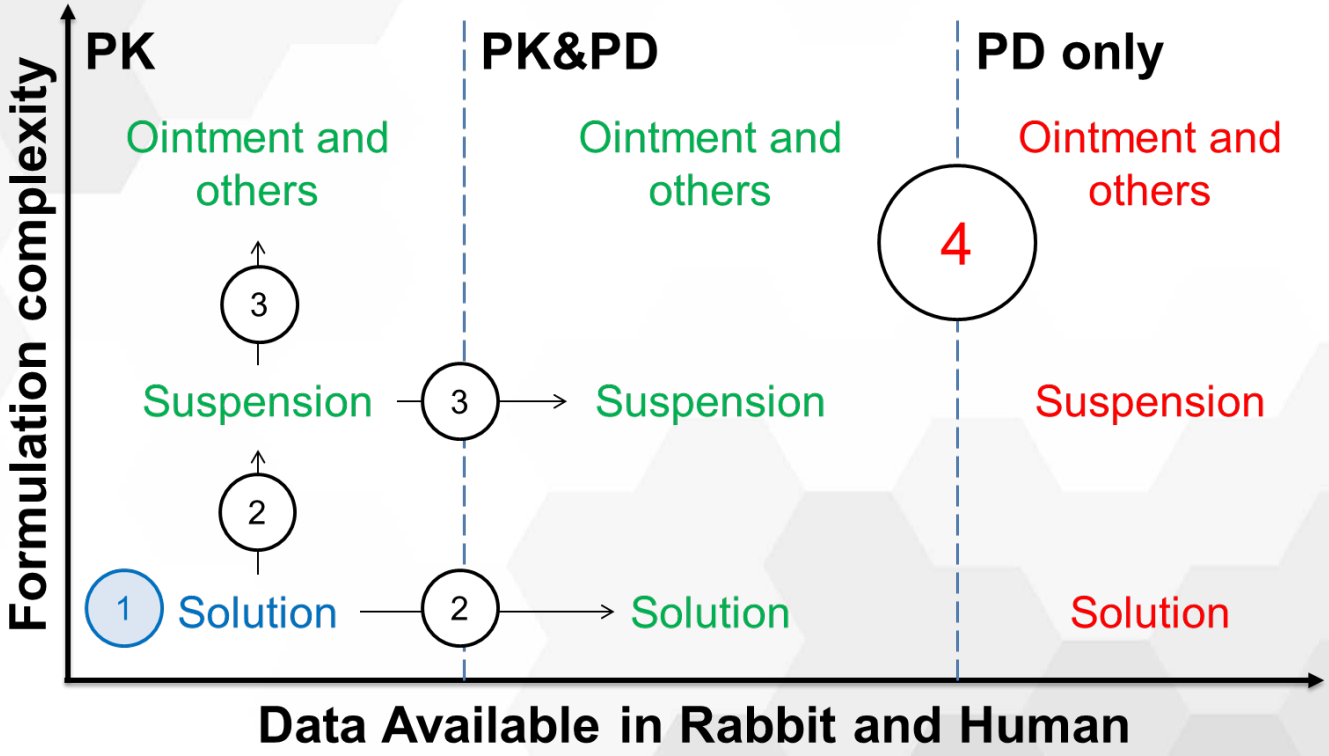
	C_{max} (µg/mL)		$AUC_{0\rightarrow3}$ (µg.h/mL)	
	Observed	Simulated	Observed	Simulated
TOBRADEX ST© 0.05%	0.106 ± 0.019	0.081	0.191 ± 0.01	0.13
TOBRADEX© 0.1%	0.069 ± 0.022	0.06	0.118± 0.006	0.095



Model Application



What can we do using PBPK model?


PK
PK&PD
PD only
Formulation complexity
Ointment and others
Ointment and others
Ointment and others
4
3
Suspension
3
Suspension
Suspension
2
1
Solution
2
Solution
Solution
Data Available in Rabbit and Human

Clinical Ocular Exposure Extrapolation Using PBPK

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SimulationsPlus MIDD+22 Model Informed Drug Development

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 ophthalmic formulations
- Identifying the impact of any differences in manufacturing, formulation, or physicochemical characteristics between a generic ocular drug product and its reference listed 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 and a burden for generic development
- 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 levofloxacin (Lev) administered as an ophthalmic solution in rabbits
- To predict Lev clinical ocular exposure following topical administration in patients undergoing cataract, virectomy, keratoplasty, and corneal transplant surgeries

METHODS

- All simulations were performed using GastroPlus® (Version 9.8 Simulation Plus Inc., Lancaster, CA, USA)
- Ocular Compartmental Absorption and Transit (OCAT™) model was used to build a MAM for Lev ophthalmic solution. The OCAT accounts for nasolacrimal drainage, ocular absorption, and distribution in the eye
- Cornea epithelium and conjunctiva permeabilities 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 Lev exposure in humans by adjusting the physiological parameters to match human ocular physiology. All of Lev specific parameters were kept constant between rabbit and human simulations

RESULTS

Table 1: Summary of pre-clinical studies used for Lev solution OCAT model development and validation in rabbit

Study	Species	BW (kg)	Gender	Doses	Dose Frequency	Volume (µL)
A	Japanese White	2.25	both	1.50%	single	30
B	New Zealand	2.75	N/A	0.50%	4 times per 10min	50
C	New Zealand	2.5	female	1.50%	single	50
D	New Zealand	2.3	female	1.50%	single	50
E	New Zealand	2.75	male	0.50%	3 times per 15min	50
F	Dutch Belted	2	male	0.50%	single	50

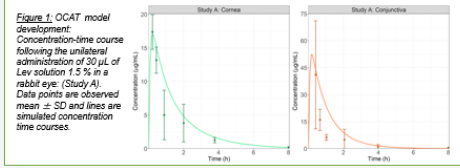

Figure 1: OCAT model development: Concentration-time course following the unilateral administration of 30 µL of Lev solution 1.5 % in a rabbit eye: (Study A). Data points are observed mean ± SD and lines are simulated concentration time courses.

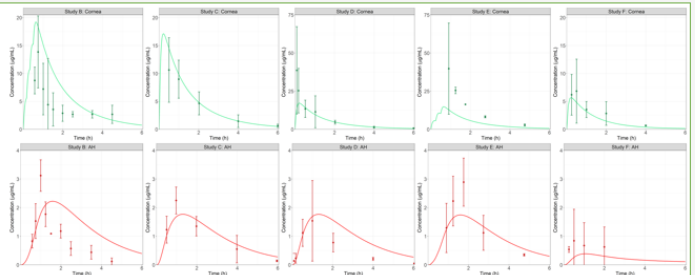

Figure 2: OCAT model validation: Concentration-time course following administration of Lev solution in a rabbit eye. Study designs are presented in Table 1: (Study B, C, D, E, F). AH: Aqueous humor. Data points are observed mean ± SD and lines are simulated concentration time courses.

Table 2: Summary of clinical studies used for human extrapolation to predict clinical ocular exposure following topical (solution) and PO Lev administration

Study	Surgery	ROA	Doses	Dose Frequency	Volume (µL)
A	Cataract	Topical	0.5%	15, 30, 45, 60 min before surgery	39
B	Cataract	Topical	0.5%	15, 30, 45, 60 min before surgery	39
C	Cataract	Topical	0.5%	60, 75, 90 min before surgery	39
D	keratoplasty	Topical	0.5%	60, 75, 90 min before surgery	39
E	corneal transplant	Topical	1.5%	15, 10 min before surgery	39
F	keratoplasty	Topical	0.5%	60, 75, 90 min before surgery	39
G	Virectomy	Topical	0.5%	3 doses the day before surgery, 20, 40, 60, 80, 100, 120 min before surgery	39
H	Virectomy	PO	750 mg	-	-
I	Virectomy	PO	200 mg	3 doses the day before surgery, 180 min before surgery	-

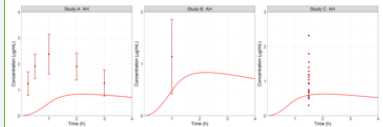

Figure 3: Human extrapolation for patients undergoing cataract surgery: Concentration-time course following the unilateral administration of 39 µL of Lev solution 0.5 % in patients (Study A, B, C). Data points are observed mean ± SD and lines are simulated concentration time courses.

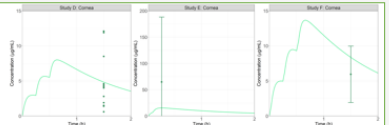

Figure 4: Human extrapolation for patients undergoing keratoplasty or corneal transplant surgeries: (Study D, E, F). Data points are observed mean ± SD and lines are simulated concentration time courses.

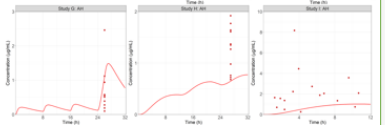

Figure 5: Human extrapolation for patients undergoing virectomy surgery following topical (Study G) or PO administrations (Study H, I). Data points are observed mean ± SD and lines are simulated concentration time courses.

CONCLUSION

- Preliminary data suggest that the OCAT model reasonably predicts human ocular exposure once validated with rabbit ocular PK data for solutions
- The model reasonably predicts observations sampled from patients with cataract, virectomy, keratoplasty, and corneal transplant 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 levofloxacin 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

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Disclaimer: This poster reflects the views of the authors and should not be construed to represent the FDA's views or policies.

FDA

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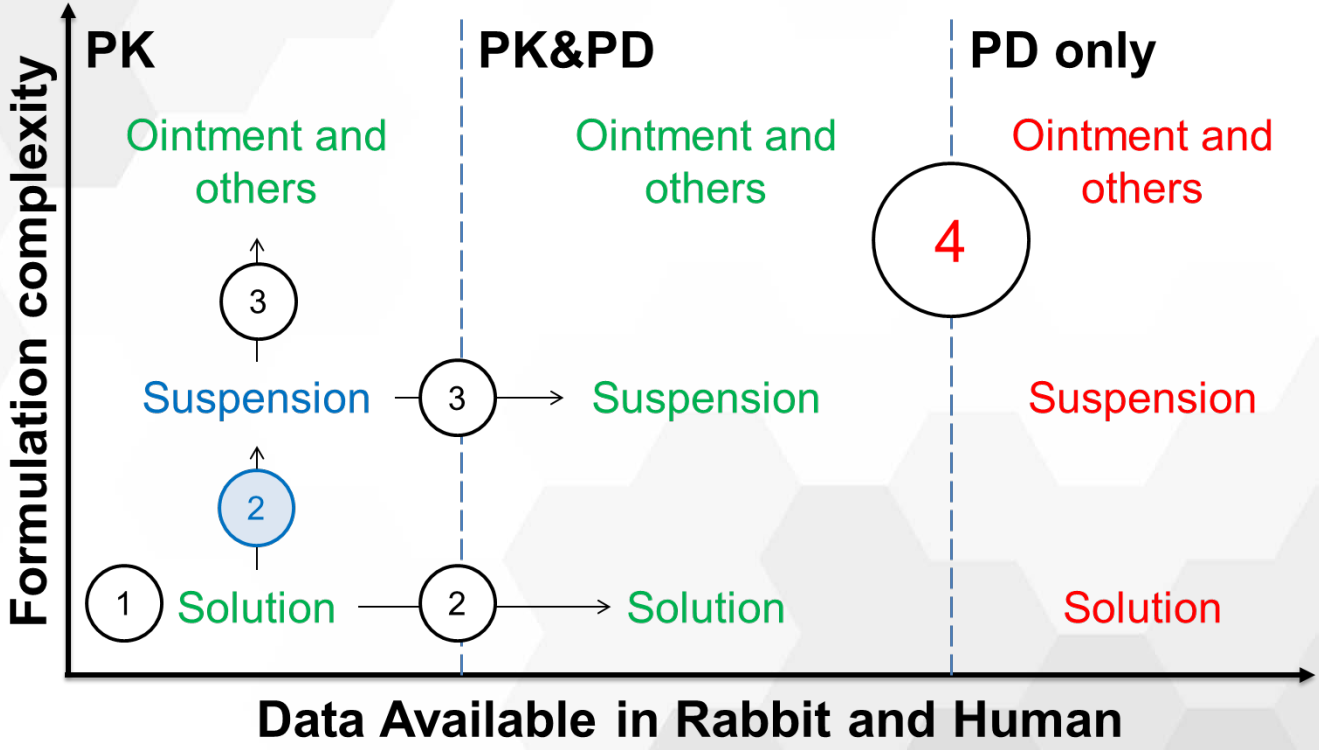
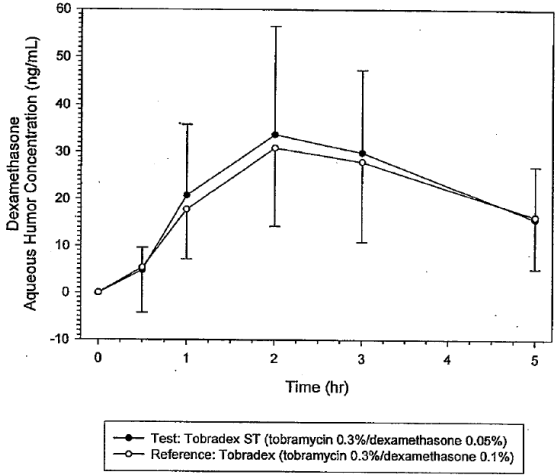
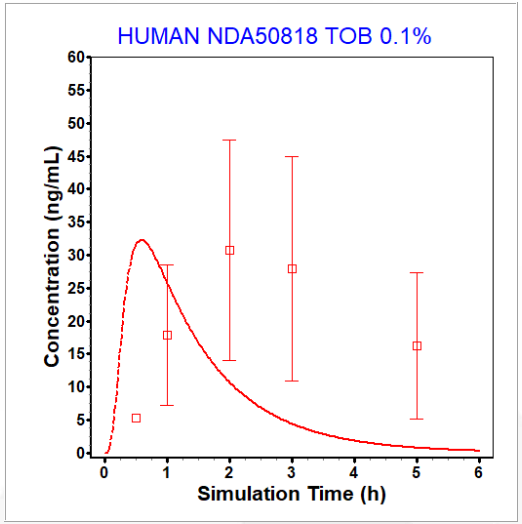
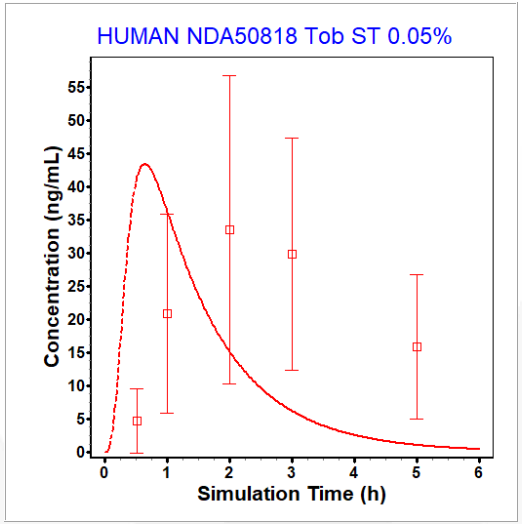

PK
PK&PD
PD only
Formulation complexity
Ointment and others
Ointment and others
Ointment and others
3
4
Suspension
3
Suspension
Suspension
2
1
Solution
2
Solution
Solution
Data Available in Rabbit and Human

Figure 2.2.3-1. Mean Dexamethasone Aqueous Humor Concentrations Versus Time from Cataract Patients Following a Single Unilateral Topical Ocular Dose of Tobramycin 0.3%/Dexamethasone 0.05% or TOBRADEX (Per Protocol Analysis)

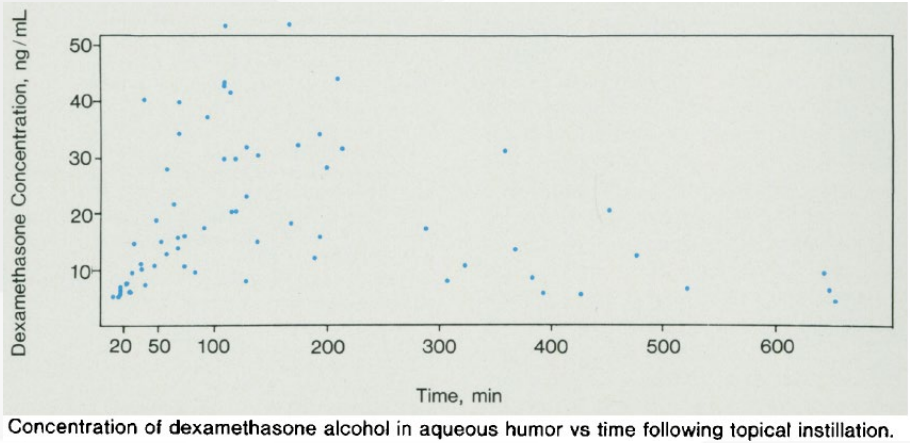






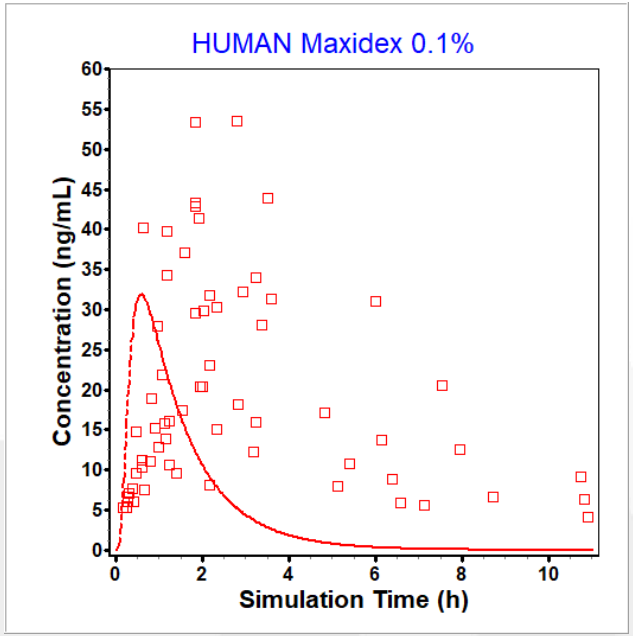
Formulation characteristics

Formulation	TOBRADEX ST®f	TOBRADEX®f	
Strength (Dex)	0.05%	0.1%	
Viscosity	72.7	1.7	cP
Mean PS	3.87	3.08	µm



Concentration of dexamethasone alcohol in aqueous humor vs time following topical instillation.

Watson 1988 Penetration of topically applied dexamethasone alcohol into human aqueous humor



Conclusion

- LAD bioequivalence presents challenges compare to oral drug products
- PBPK model can support bioequivalence assessment of LAD
- Research on PBPK models for ophthalmic formulations started more than 10 years ago and is still ongoing
- Preclinical to clinical extrapolation validation is mandatory
- Early results are encouraging !
- The approach described in this presentation is expected to have a significant impact on ophthalmic generic drug product development

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Model Informed Drug Development

Q&A

Questions & Answers