SimulationsPlus

PBPK Models of Complex Injectable and Ophthalmic Drug Products: Case Studies

Maxime Le Merdy, PharmD, PhD

Associate Director, Research and Collaboration

12/8/2023

PBPK model

PBPK: Physiologically Based Pharmacokinetic Model

System/Physiology:
- Height, BW, BMI
- Tissue sizes & blood flows
- Tissue compositions
- Enzyme &transporters
- Others…

Formulation:
- Dose, Dosage form
- Particle size & CQAs
- Release profiles

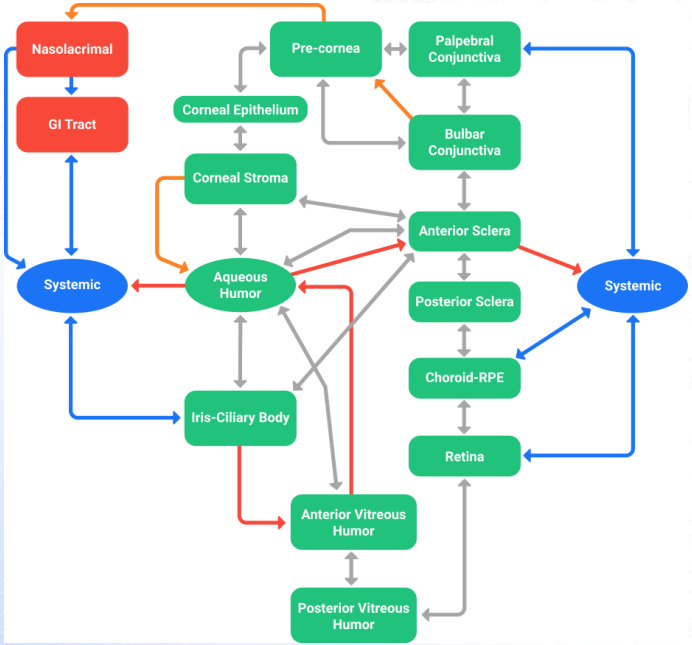
Compound:
- LogP/logD, pKa(s)
- Permeabilities
- Fup and Fut
- Clearances
- Others…

PBPK

Prediction of APIs PK in plasma and tissues

Ocular PBPK Model

SimulationsPlus



Validation of preclinical to clinical extrapolation using the OCAT™ model

Preclinical

NZ

Development and validation of ocular model to desribe exposure in NZ rabbits.

DB

Characterization of melanin binding using data in DB rabbits.

Clinical

Prediction of ocular PK in human.

SimulationsPlus

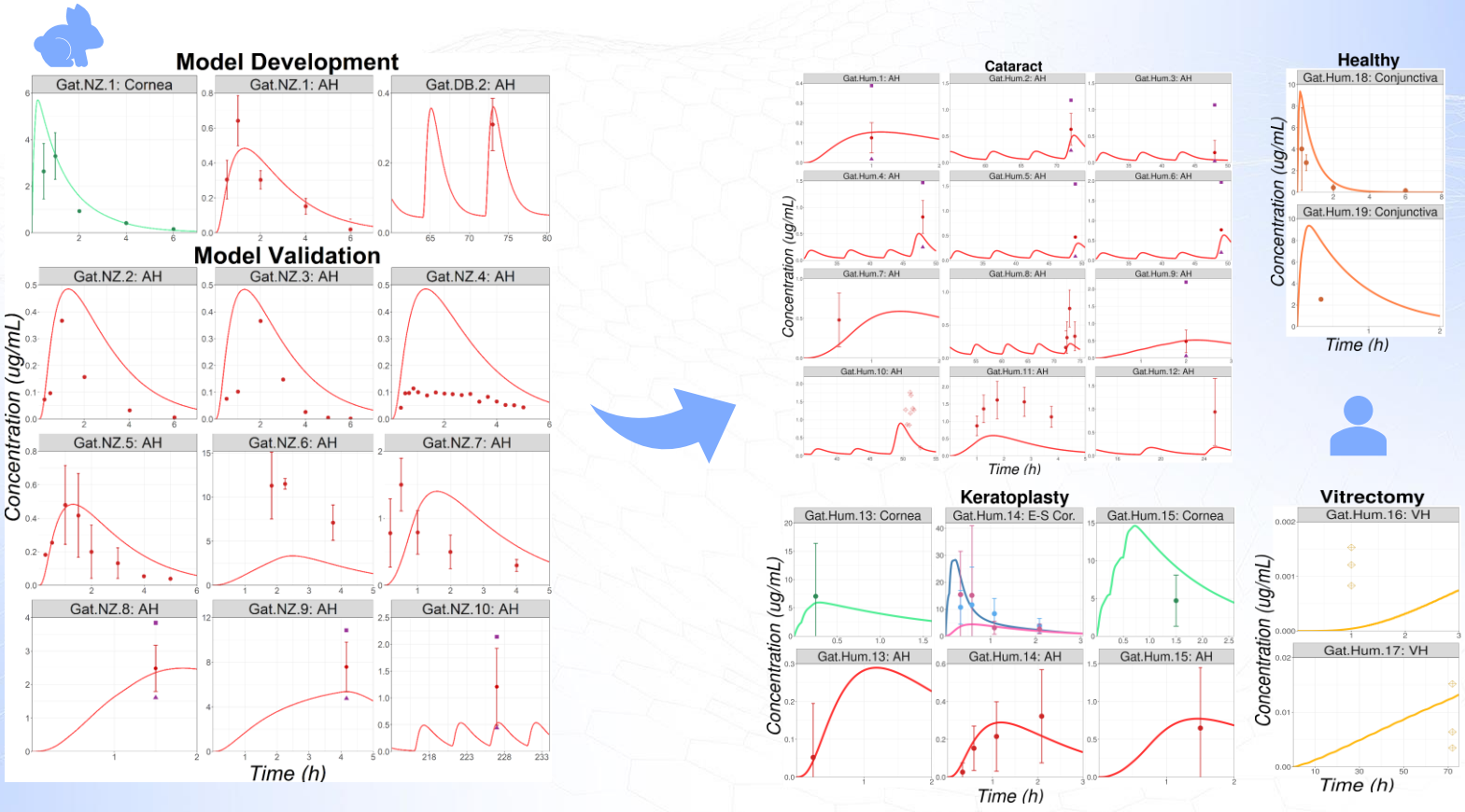
Pharmaceutical Research
https://doi.org/10.1007/s11095-022-03390-z

ORIGINAL RESEARCH ARTICLE

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

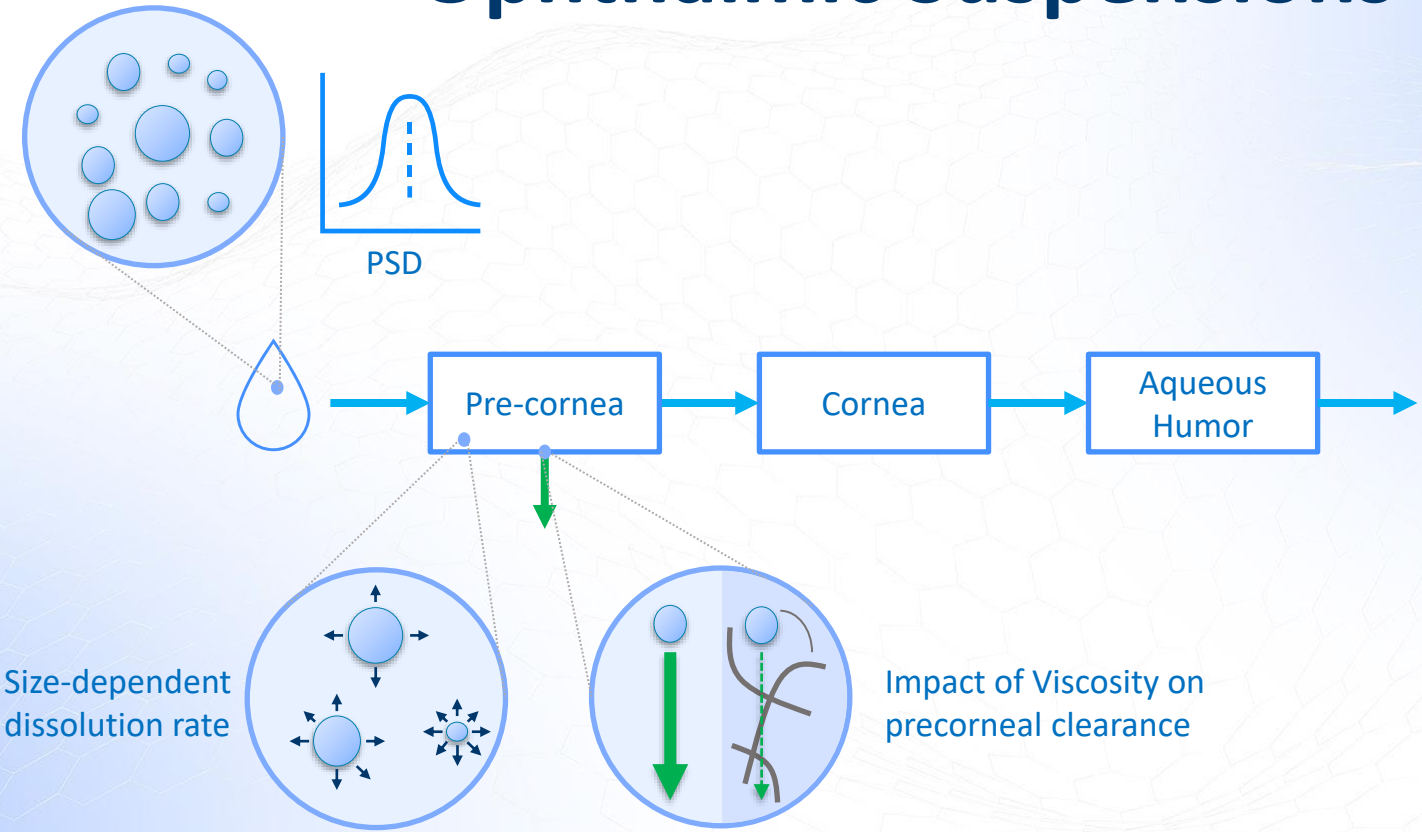
Maxime Le Merdy[1] · Farah AlQaraghuli[1] · Ming-Liang Tan[2] · Ross Walenga[2] · Andrew Babiskin[2] · Liang Zhao[2] · Viera Lukacova[1]

Gatifloxacin

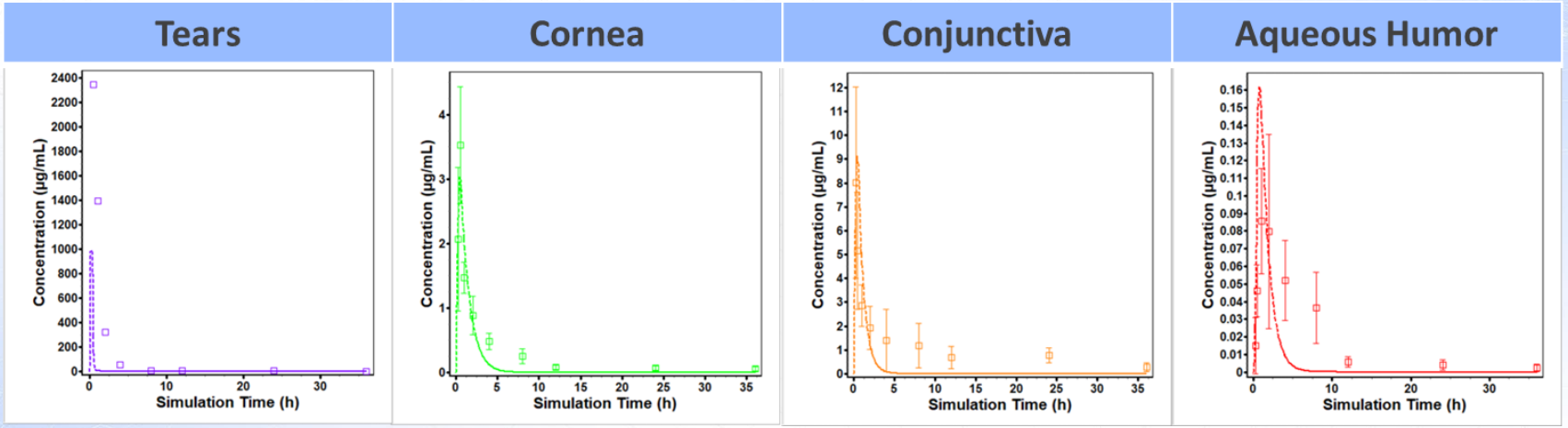


SimulationsPlus

Ophthalmic Suspensions



Besifloxacin Topical Suspension

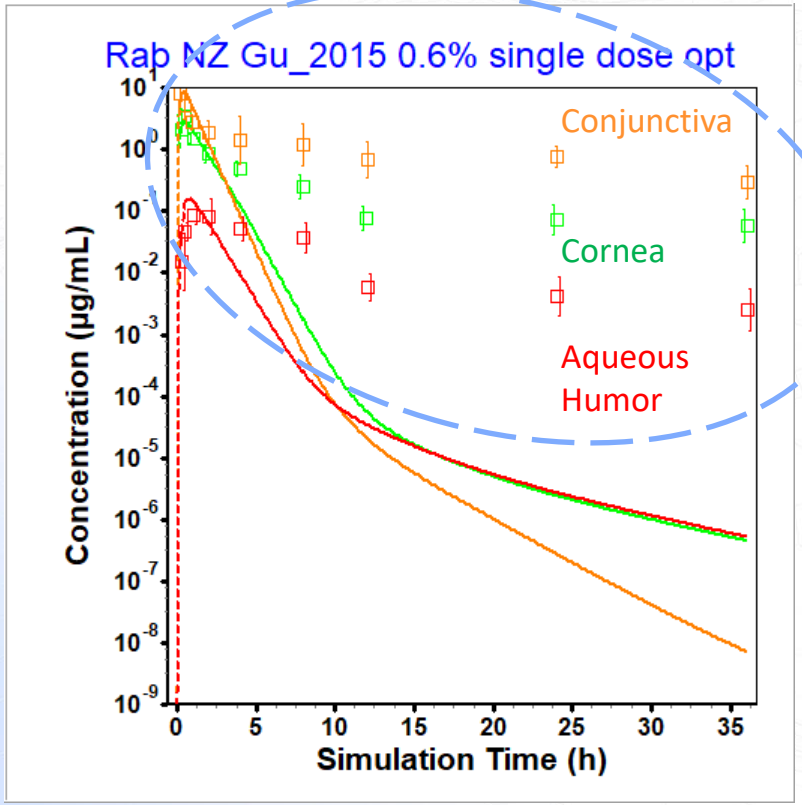


Correct prediction of the first part of the observed concentration-time courses

But…

SimulationsPlus

Besifloxacin Topical Suspension

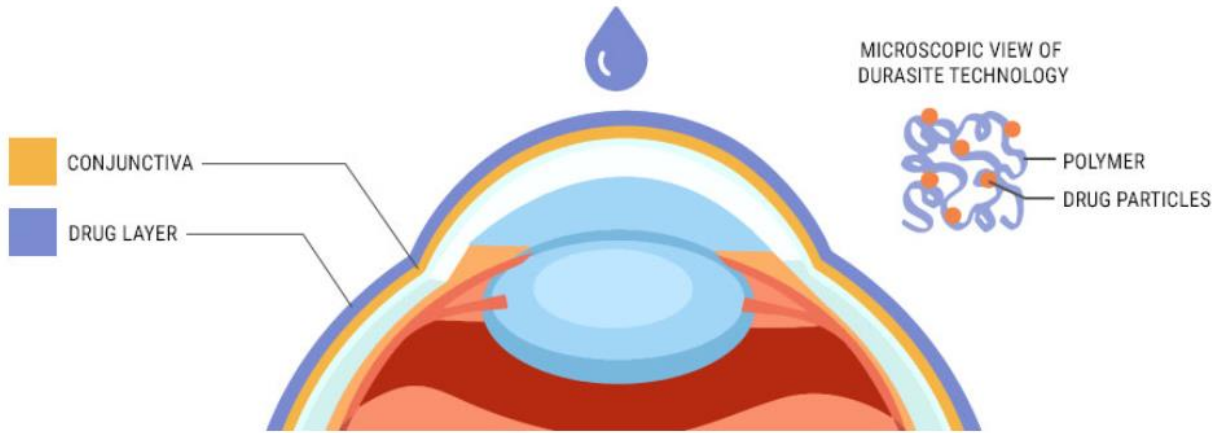


Misprediction of the second part of the observed concentration-time courses

Besivance®

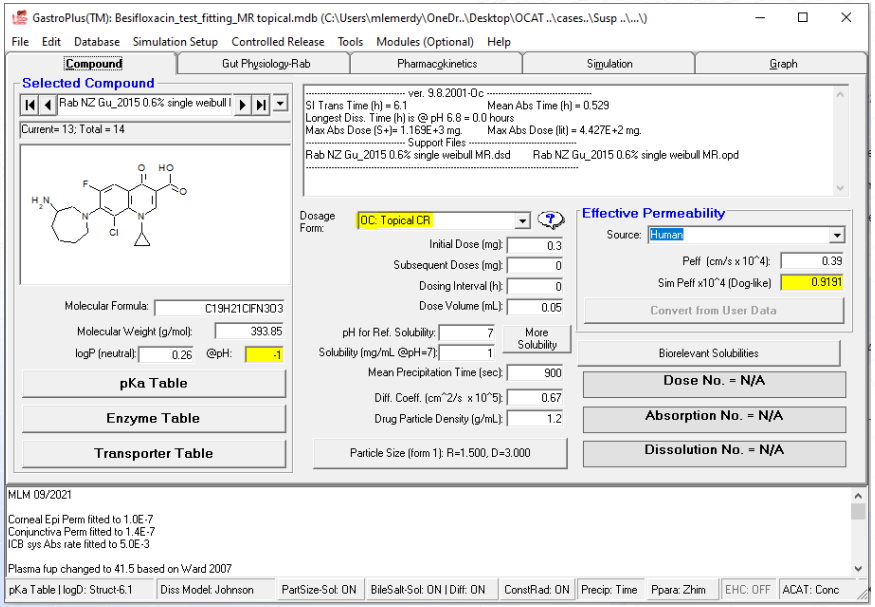
Home » MOA » **DuraSite Technology**

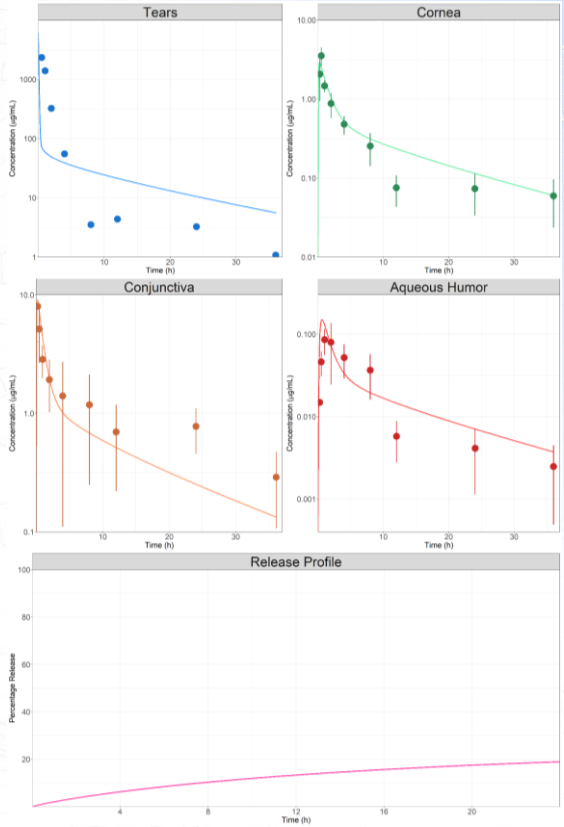
BESIVANCE IS FORMULATED WITH DURASITE TECHNOLOGY



- BESIVANCE uses DuraSite technology to help ensure the active molecule, besifloxacin, remains on the ocular surface to fight pathogens [1-3]
- With DuraSite, besifloxacin particles are suspended within a mucoadhesive polymer, providing long-lasting coverage with every drop [1-3]
- BESIVANCE clinical studies have shown that besifloxacin resides on the ocular surface for **up to 12 hours** [3]

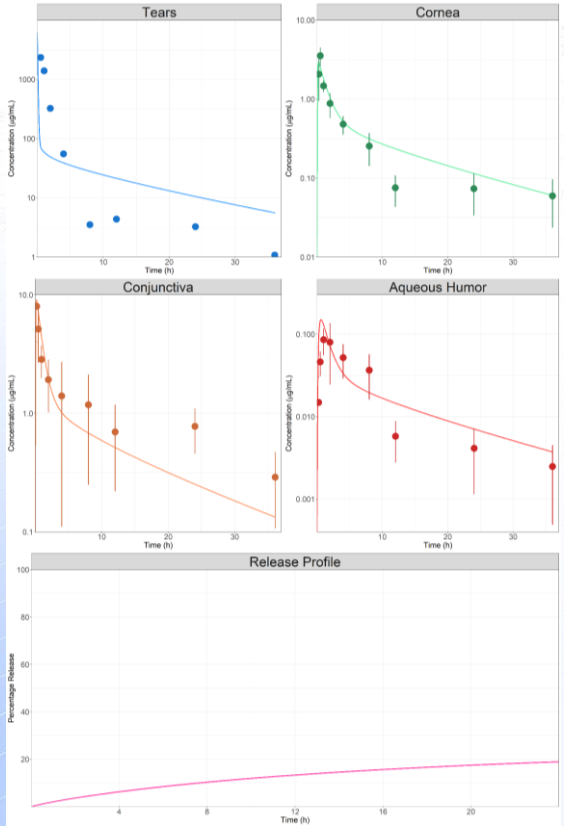
Besifloxacin Topical Suspension

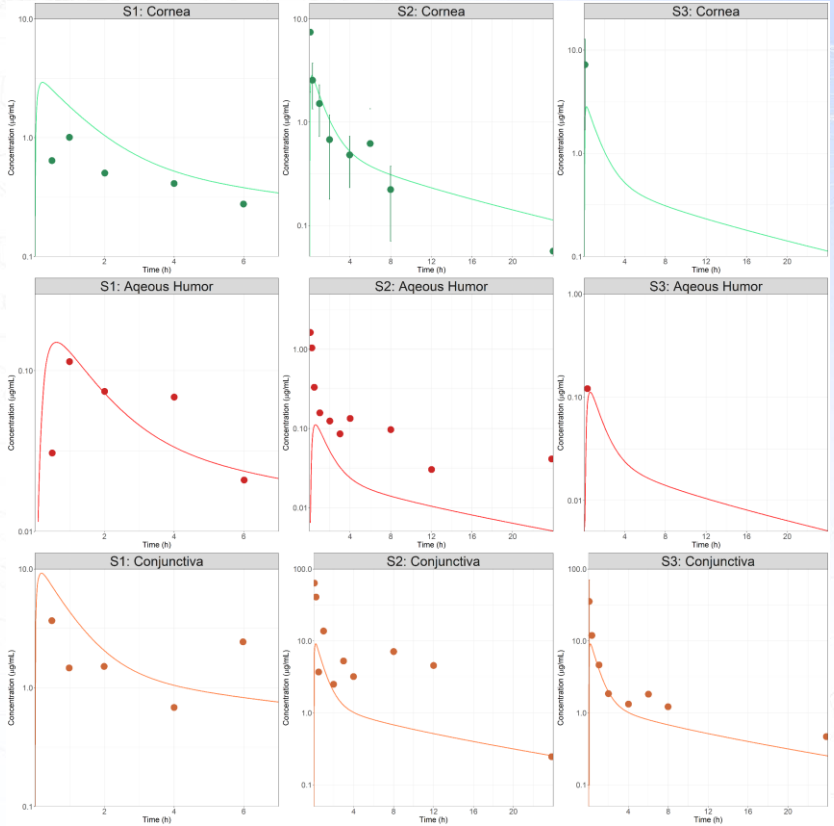




Model development successful using a new dosage form lumping all CQAs into one release profile

Besifloxacin Topical Suspension

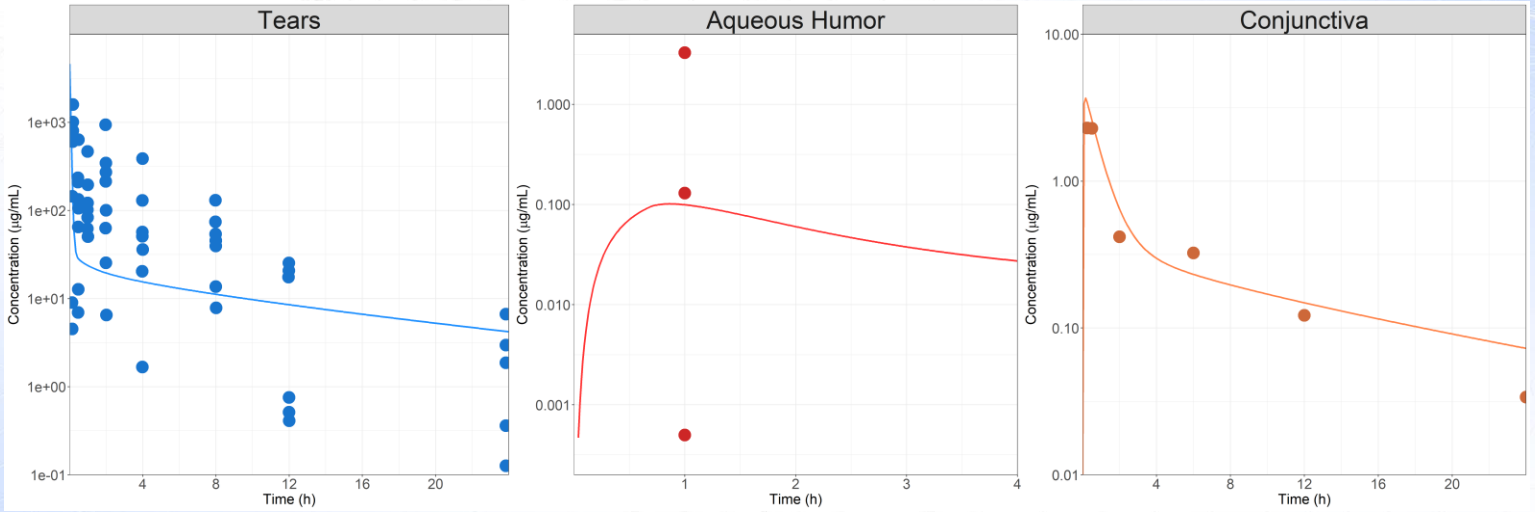




Successful Model Validation

SimulationsPlus

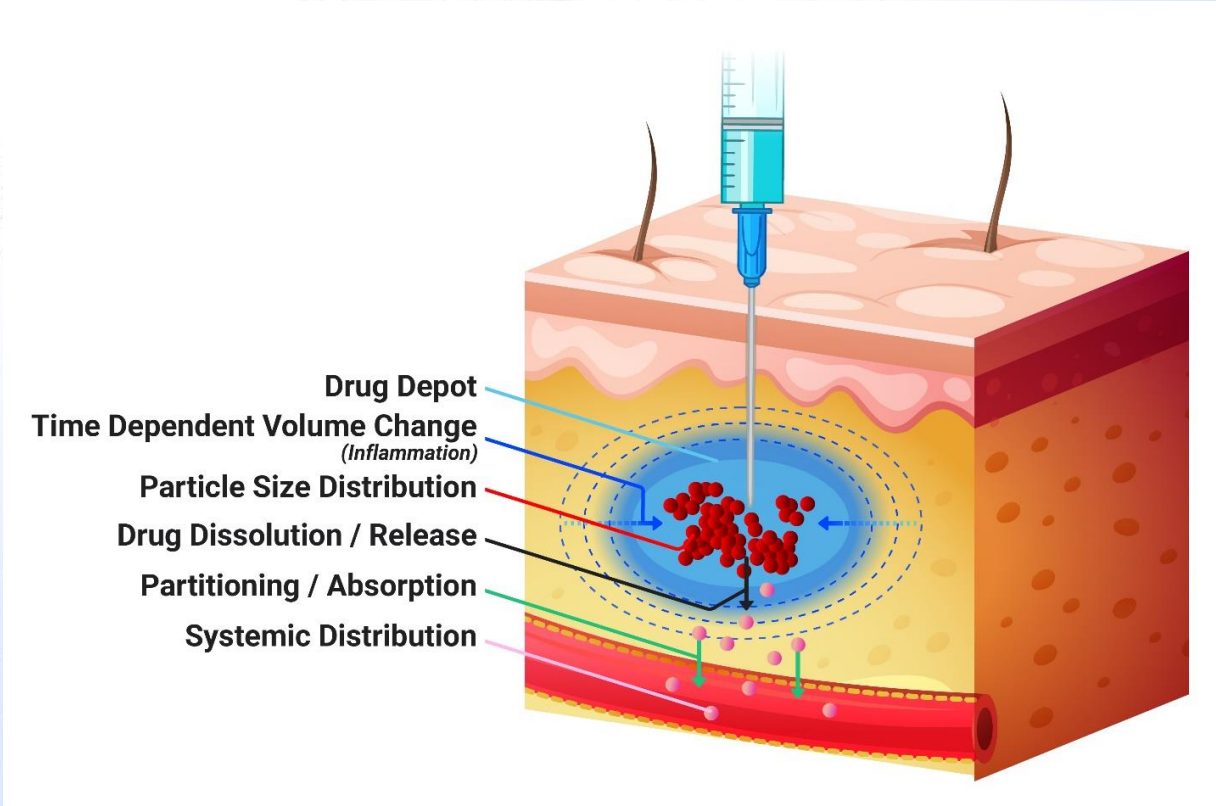
Besifloxacin Topical Suspension



Successful PBPK-based clinical Extrapolation

Long-Acting Injectable PBPK Model

LAI model



Medroxyprogesterone Acetate Case Study

Development of *in vitro-in vivo* correlations for long-acting injectable suspensions

Quanying Bao [a,2], Xiaoyi Wang [a,1], Bo Wan [a], Yuan Zou [b], Yan Wang [b], Diane J. Burgess [a,*]

[a] *University of Connecticut, School of Pharmacy, Storrs, CT 06269, USA*
[b] *Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, FDA, Silver Spring, MD 20993, USA*

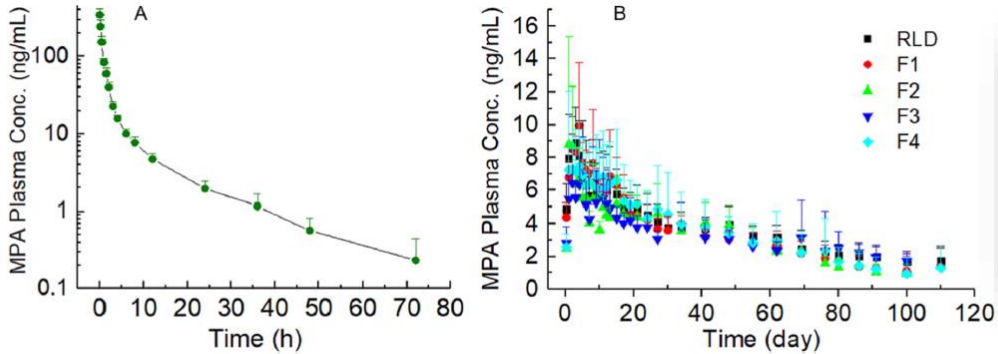


Fig. 2. The PK profiles (plasma concentration time curve, rabbit model) of: A) intravenous injection of MPA drug solution in DMSO; and B) subcutaneous injection of all prepared compositionally equivalent formulations and the RLD (n = 6, mean ± SD).

Table 2
Volume weighted particle size and size distribution of four compositionally equivalent MPA suspensions and the RLD (n = 3, mean ± SD) (Bao et al., 2022; Bao et al., 2021).

Formulation	Dv10 (μm)	Dv50 (μm)	Dv90 (μm)	Span
F1	7.21 ± 0.42	13.40 ± 0.54	24.09 ± 0.74	1.26 ± 0.04
F2	8.73 ± 0.31	21.73 ± 0.28	41.08 ± 0.53	1.49 ± 0.04
F3	0.69 ± 0.33	3.67 ± 0.43	10.13 ± 0.99	2.61 ± 0.44
F4	7.00 ± 0.13	13.03 ± 0.23	23.44 ± 0.37	1.26 ± 0.01
RLD	10.37 ± 0.99	18.23 ± 1.36	30.61 ± 1.78	1.11 ± 0.05

UCONN
UNIVERSITY OF CONNECTICUT

IV MPA Acetate

Rabbit PBPK model

Blood/plasma Conc Ratio: 0.83

Use Exp Plasma Fup [%]: 12

Use Adj Plasma Fup [%]: 4.1387

PBPK Summary

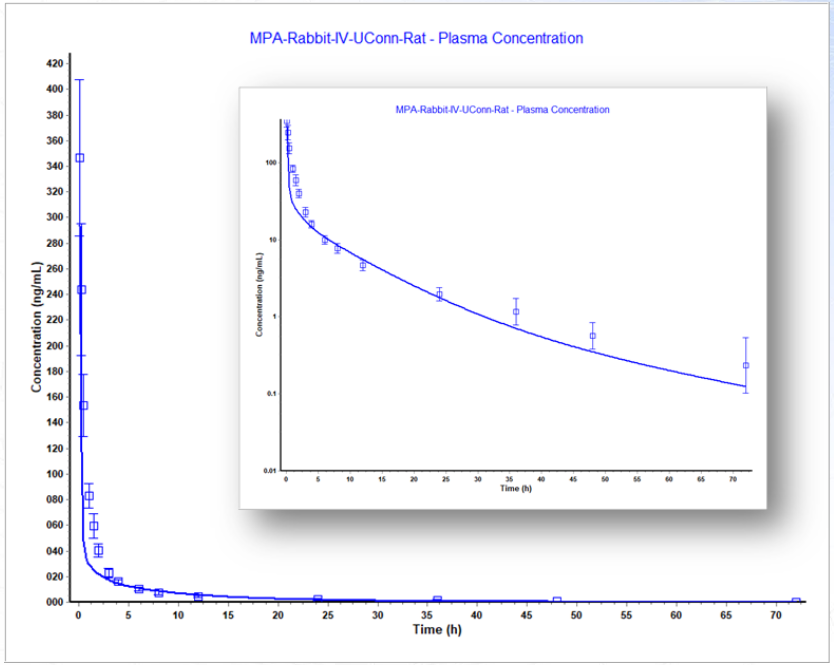
Tissue	Kp	CL	CLint	Fut/FuInt
Hepatic Artery	0.00	0.000	0.000	0.000
Arterial Supply	0.00	0.000	0.000	0.000
Venous Return	0.00	0.000	0.000	0.000
ACAT Gut	0.00	0.000	0.000	0.000
Lung	20.71	0.000	0.000	0.006
Muscle	10.13	0.000	0.000	0.012
Liver	18.16	8.767	2569.1	0.007
Spleen	9.33	0.000	0.000	0.013
Heart	13.92	0.000	0.000	0.009
Brain	43.84	0.000	0.000	0.003
Kidney	16.54	0.056	0.000	0.007
Skin	23.26	0.000	0.000	0.005
ReproOrg	16.47	0.000	0.000	0.007
RedMarrow	22.26	0.000	0.000	0.005
YellowMarrow	83.11	0.000	0.000	0.001
RestOfBody	9.37	0.000	0.000	0.013
Adipose	83.11	0.000	0.000	0.001

CLsys (L/h): 8.823

Vss (L): 51.166

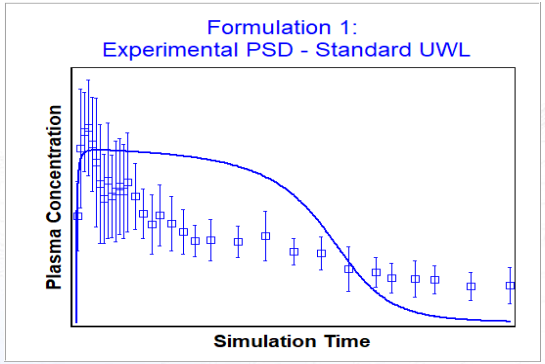
Thalf (h) 4.019

Calc Kps: Perf Kp: Lukacova; Perm Kp: Poulin-ext
Perf Fut: S+9.5; Perm FuExt: S+9.5; FuInt: S+9.5;

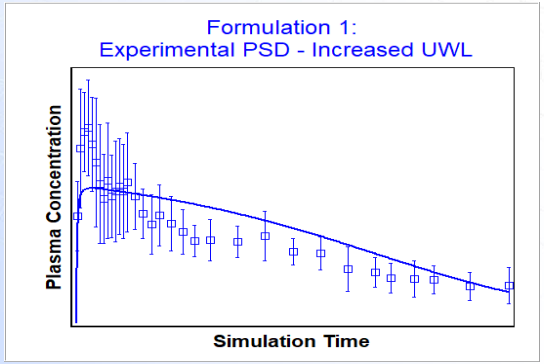


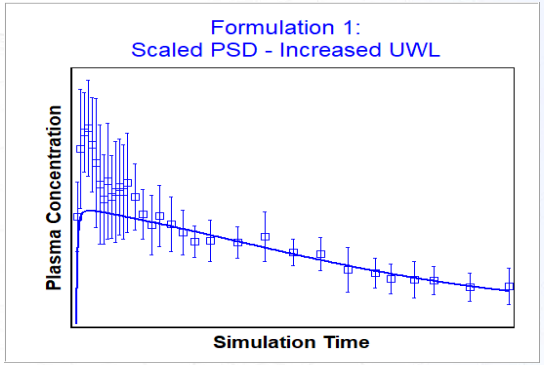
SimulationsPlus

SubQ MPA LAI suspensions



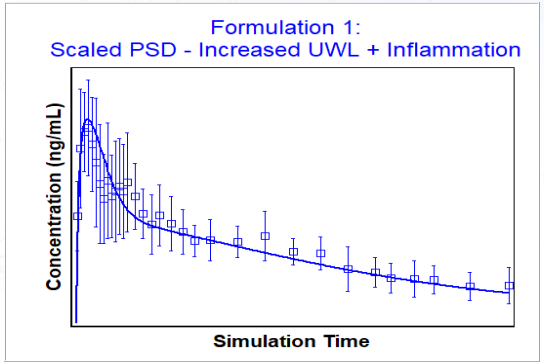
Increasing diffusion layer thickness had a significant impact on the shape of the Cp-time profile



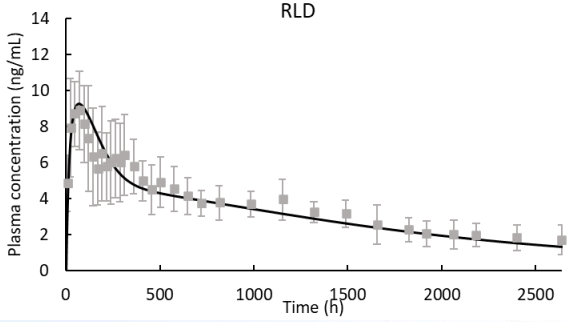


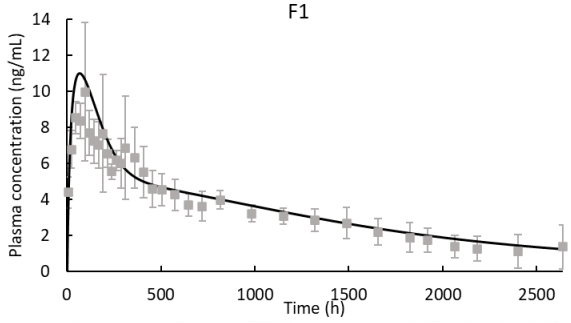
Scaling PSD further improved the shape of the profile but Cmax was still underpredicted

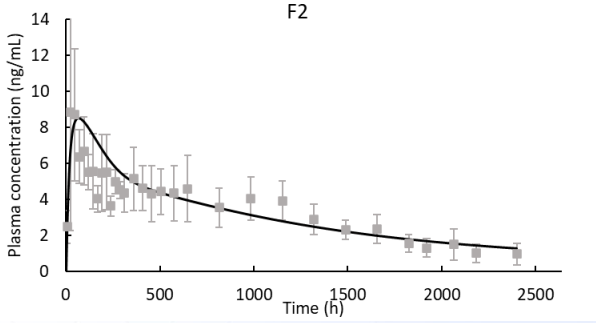
Incorporating inflammation (~3-fold increase in depot volume in 2-3 days after injection) improved prediction of Cmax

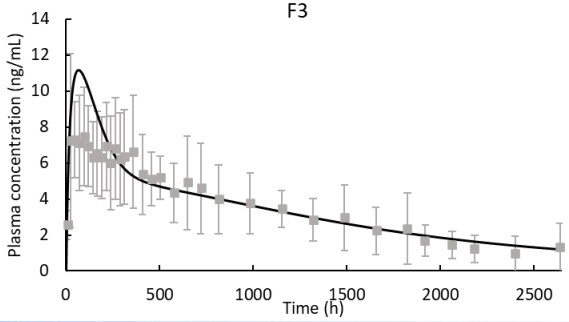


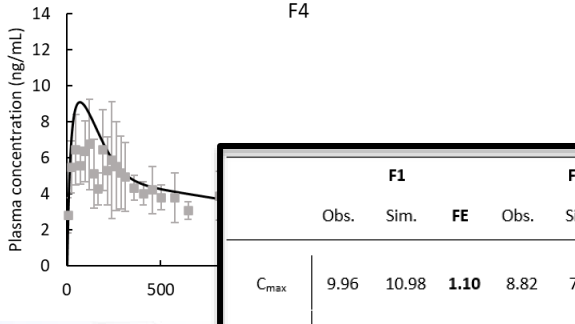
SubQ MPA LAI suspensions







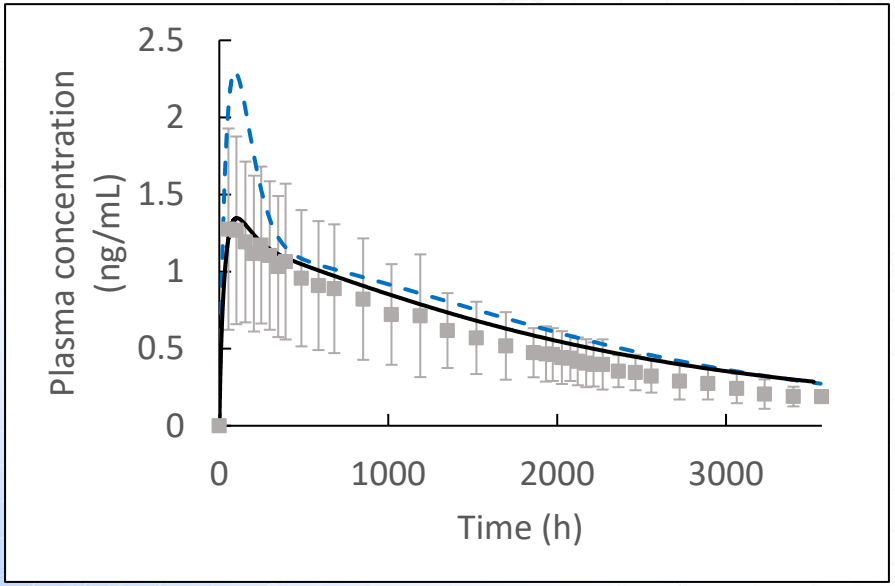




	F1			F2			F3			F4			RLD		
	Obs.	Sim.	**FE**	Obs.	Sim.	**FE**	Obs.	Sim.	**FE**	Obs.	Sim.	**FE**	Obs.	Sim.	**FE**
C_{max}	9.96	10.98	**1.10**	8.82	7.72	**0.88**	7.46	11.13	**1.49**	6.75	9.107	**1.35**	8.9	9.28	**1.04**
AUC_{0-t}	8435	9193	**1.09**	7659	7273	**0.95**	8714	9245	**1.06**	7779	8343	**1.07**	9229	8730	**0.95**

C_{max} in ng/mL; AUC in ng-h/mL; RLD: Reference Listed Drug; FE= Fold-error (Simulated/Observed).

SubQ MPA - Human predictions



Simulated (lines) and observed (symbols) plasma concentration time course following SC administration of Depo-subQ Provera 104® in humans.

Blue line: predictions with the same parameters as used in the rabbit model; Black line: Adjusted diffusion layer thickness and inflammation scaling factor.

PBPK model prediction statistics for the RLD following SC administration in humans

		Observed	Simulated	FE
Same as Rabbit	C_{max}	1.276	2.289	1.79
	AUC_{0-t}	2005.5	2680	1.34
Updated model	C_{max}	1.276	1.347	1.06
	AUC_{0-t}	2005.5	2360.8	1.18

Cmax in ng/mL; AUC in ng-h/mL; FE= Fold-error (Simulated/Observed)

Conclusions

Ocular PBPK model:

- Ocular PBPK models present an interesting approach to support the regulatory assessment of complex generic drug products
- Better identification of formulations' CQAs, and excipients impact, are mandatory to improve model predictions

LAI PBPK model:

- LAI PBPK models help to understand the impact of physiological responses on PK profiles
- Additional work is needed to fully understand the interaction between the physiology and formulation characteristics

➔ Due to their mechanistic structure linking formulation CQAs and physiology, PBPK models are a **unique** tool to support the regulatory assessment of complex generic drug products

Acknowledgment

Simulations Plus

Dr. Daniela Silva

Dr. Viera Lukacova

UCONN
UNIVERSITY OF CONNECTICUT

FDA

Dr. Ming-Liang Tan

Dr. Ross Walenga

Dr. Alam Khondoker

Dr. Eleftheria Tsakalozou

Dr. Andrew Babiskin

Dr. Liang Zhao

Connect with us!

LinkedIn: Simulations-Plus

Facebook: SimulationsPlus

Twitter: SimulationsPlus

YouTube: SimulationsPlusInc

LinkedIn Group: GastroPlus® User Group

SimulationsPlus