Physiologically-based pharmacokinetic modeling to support generic ophthalmic product development and regulatory decision making

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 3: Complex Injectable, Ophthalmic and Otic Products Pt. 2

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September 21, 2021

Learning Objectives

- Recognize approaches to demonstrate bioequivalence (BE) for ophthalmic generics
- Explain challenges in developing and assessing ophthalmic generics
- Utilize physiologically-based pharmacokinetic (PBPK) modeling to advance the development and approval of ophthalmic generics
- Narrow down the knowledge gaps through research projects

Topical Ophthalmic Drug Products

- Very successful in approving generic ophthalmic solution products
- Few to no approvals for complex ophthalmic generics since 1984
  - o Suspensions
  - o Ointments
  - o Emulsions

Dosage Form (2018 sales)	Number of Reference (RLD) products in USA[1]	% of RLDs that have an approved generic[2]
Solutions ($17.9B)	~111	55%
Suspension ($1.9B)	~22	23%[3]
Emulsion ($4.4B)	4	0
Ointment ($730M)	~15[4]	30%[3]

1. Includes RLD products that are no longer marketed but that can still serve as a reference drug
2. Although approved, a generic may not be currently marketed
3. Most (>75%) were approved pre-Hatch-Waxman (1984)
4. A number of ointment NDAs have been discontinued, but may be re-designated as RLD by industry request

Slide courtesy of Darby Kozak, modified

Luke M and Kozak D, *Journal of Ocular Pharmacology and Therapeutics* **37**, 157 (2021)

BE Approaches for Ophthalmic Generics

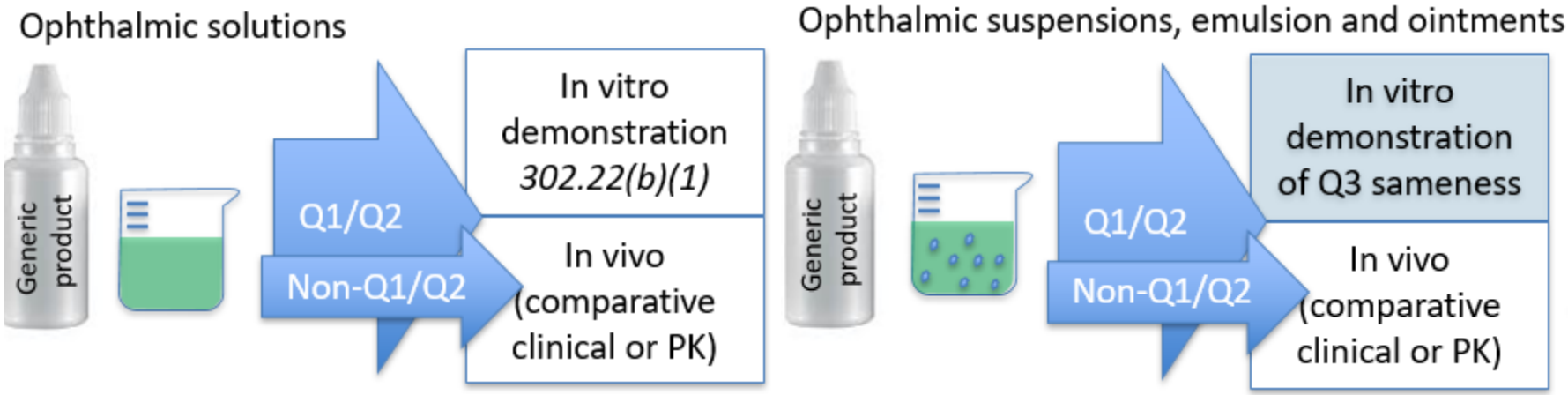
Multiple options to demonstrate BE

- In vivo local pharmacokinetic (PK) studies
- In vivo pharmacodynamic (PD) studies
- Comparative clinical endpoint (CCE) studies
- In vitro studies

Each BE option has inherent benefits, risks, and limitations

BE Approaches for Ophthalmic Generics

Different dosage forms



Slide courtesy of Darby Kozak, modified

Product-specific guidance (PSG) available, Pre-ANDA meetings, Controlled Correspondences (CC)

Challenges in Ophthalmic Generics

- Ophthalmic drugs are locally acting and drug measurements in local eye tissues are often impractical, unethical, and cost-prohibitive
- Local PK studies
  - Limited tissue available such as aqueous humor
  - Sparse sampling with high variability
  - Large sample population required
- Comparative clinical endpoint studies
  - Confounded by patient disease severity
  - Variability in measuring efficacy

Why PBPK Modeling?

- Integrate physiology, drug/drug product properties, existing in vitro and in vivo data
- Predict local PK in eye tissues and PD
- Extrapolate to human from preclinical species
- Simulate virtual BE in lieu of conducting a PD/CE BE study?

PBPK-Related Ophthalmic Research

- Internal Research
  - Perform FDA internal research to meet the regulatory scientific needs
- External Research
  - Funding Opportunity Announcement (FOA): Grants
  - Broad Agency Announcement (BAA): Contracts

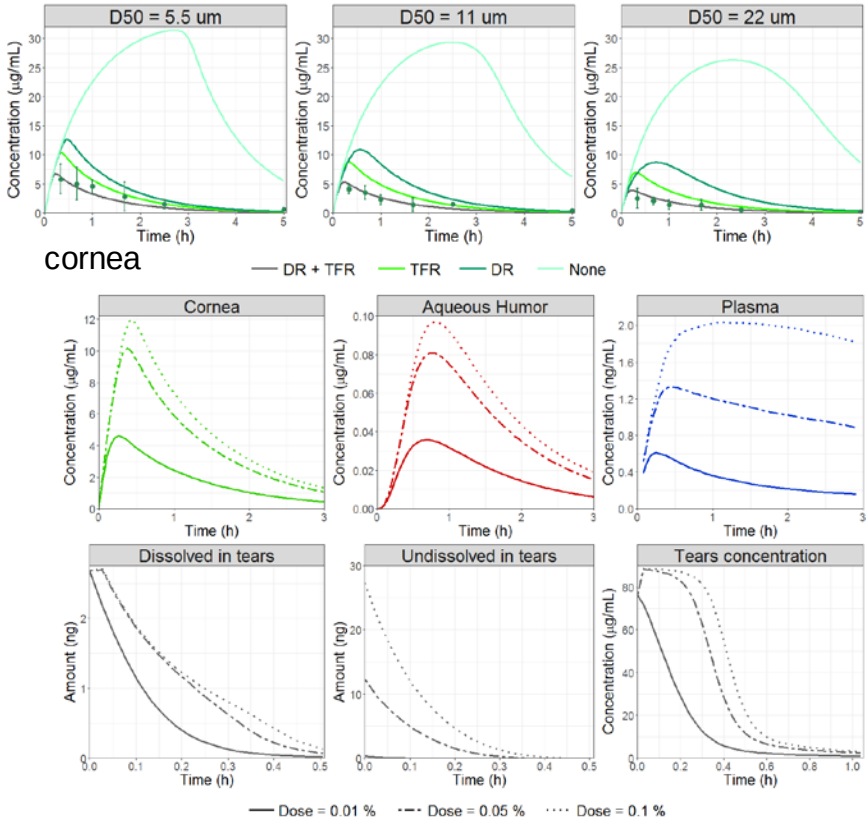
https://www.fda.gov/drugs/generic-drugs/generic-drug-research-collaboration-opportunities

Ophthalmic Suspensions

***Purpose**: Use verified rabbit OCAT™ PBPK model to study formulation effect on exposure*

- Tears dynamic impact on elimination following the administration of three suspensions of Dex 0.1% with differing particle size

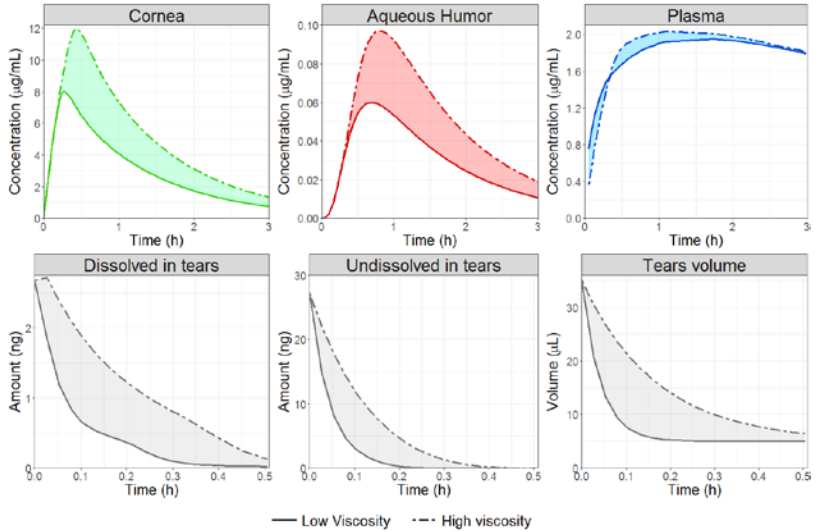
- Non-linearity of PK: simulated at three different strengths: 0.01%, 0.05% and 0.1%
  - Ocular absorption and distribution
  - Plasma exposure
  - Drug dissolved and undissolved amounts in the tear



LeMerdy, M., Tan, M. L., Babiskin, A., and Zhao, L. AAPS Journal **22**, 26 (2020)

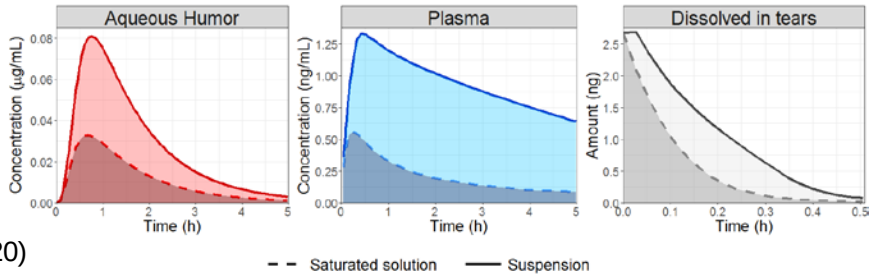
Ophthalmic Suspensions

- Role of viscosity: simulated two suspension formulations of Dex 0.1% with different viscosities
  - Concentrations in the cornea, aqueous humor, and plasma
  - Tear volume
  - Dissolved and undissolved drug amount in the tears



- Suspension and solution formulation effect on exposure

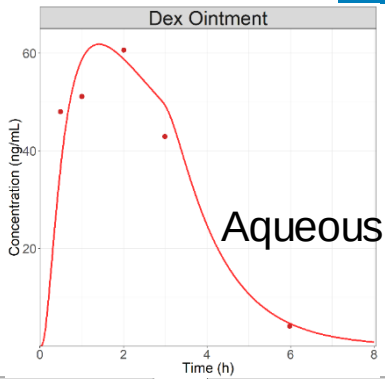
  How much does the drug in the solution contribute to the exposure relative to the total drug in solution and suspension formulations?



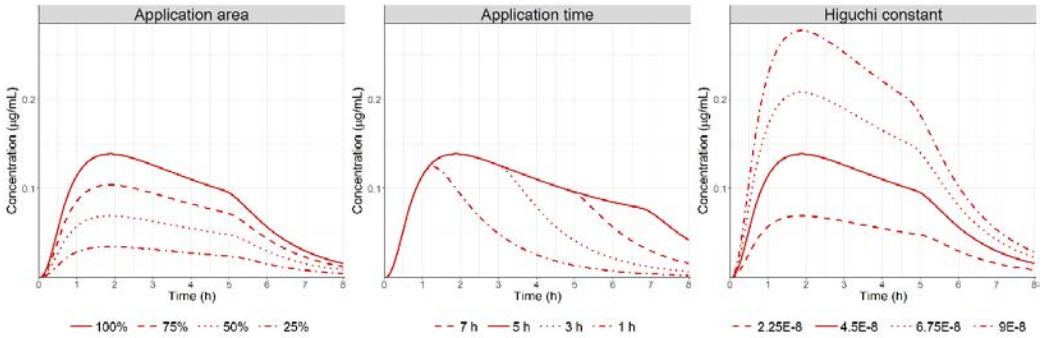
LeMerdy, M., Tan, M. L., Babiskin, A., and Zhao, L. AAPS Journal **22**, 26 (2020)

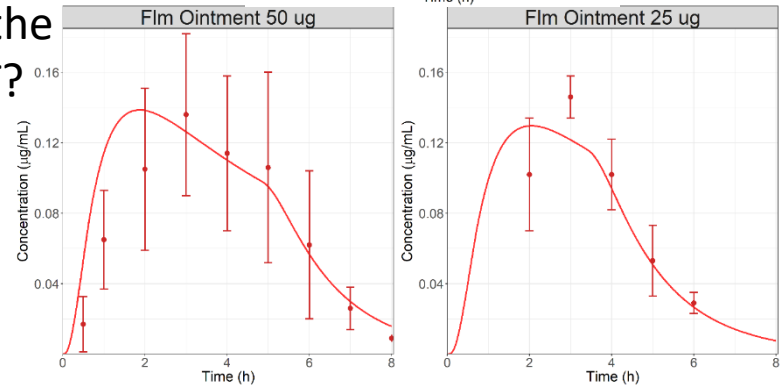
Ophthalmic Ointments

- Expanded OCAT™ model to include ocular ointment formulation
- Dexamethasone and fluorometholone ointment rabbit models
- Sensitivity of application surface area, application time, and the Higuchi release constant
- Higuchi release constant most significantly impact the ocular exposure and Cmax, biopredictive from IVRT?



Aqueous humor





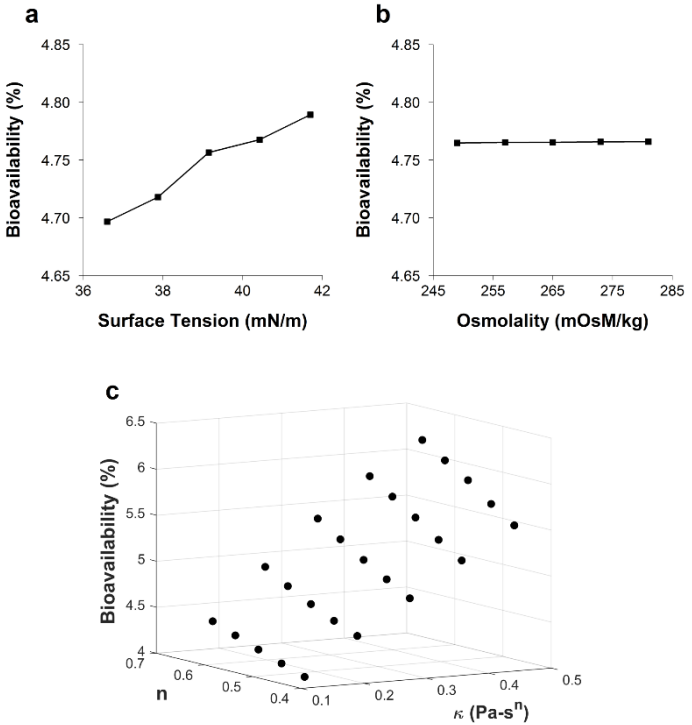
Simulations Plus, HHSF223201810255P

Le Merdy M, Spires J, Viera Lukacova V, Tan M L, Babiskin A, Xu X, Zhao L, Bolger M, *Pharm Res* **37**, 245 (2020)

Cyclosporine Emulsion Modeling

***Purpose**: impact of emulsion CQAs on product performance*

- Two internally-built models:
  - Physics/fluids-based approach to modeling tear film breakup time (TBUT)
  - Compartmental-based approach to predict bioavailability
- Studied impact of surface tension, osmolality, and power law viscosity on conjunctival bioavailability (figure at right) and TBUT
- Viscosity had the greatest influence on both outcomes

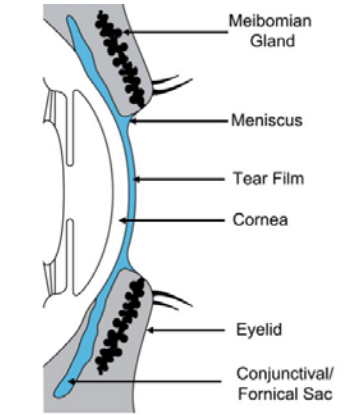


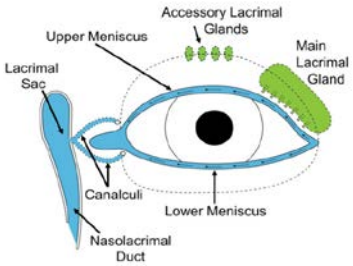
CQA: critical quality attribute

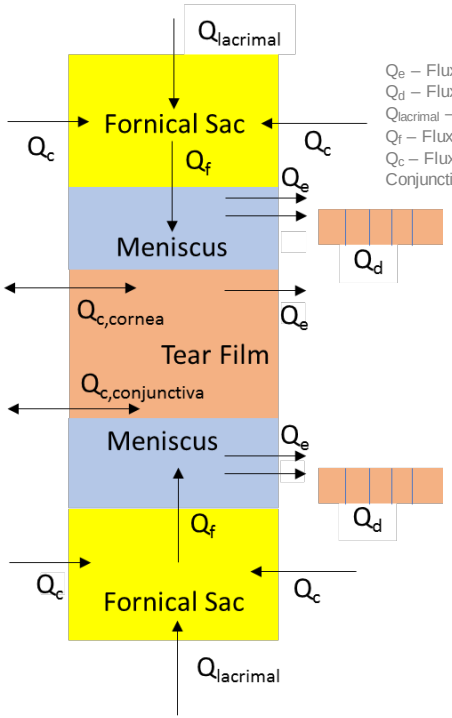
Walenga et al, *J Pharm Sci* 108, 620 (2019)

Ocular Tear Films Models

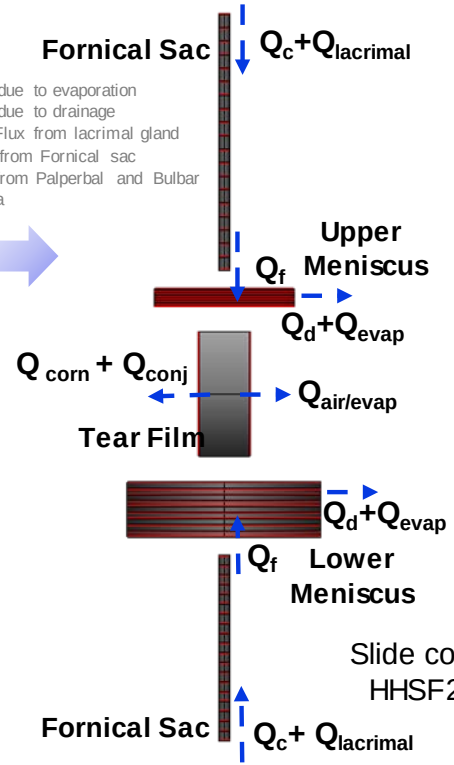
Tear Film Anatomy → ***CoBi-Compartment*** → ***CoBi-Q3D***







Q_e – Flux due to evaporation
Q_d – Flux due to drainage
$Q_{lacrimal}$ – Flux from lacrimal gland
Q_f – Flux from Fornical sac
Q_c – Flux from Palperbal and Bulbar Conjunctiva



Slide courtesy of CFD RC
HHSF223201810151C

Tear film models (with accurate anatomical description and blink dynamics) are developed for simulating drug delivery and transport using CoBi-Compartment and CoBi-Q3D capabilities.

Cyclosporine Emulsion Model Validation

Rabbit Tear Film Measurements to verify the model

- **Internal collaboration with OTR**

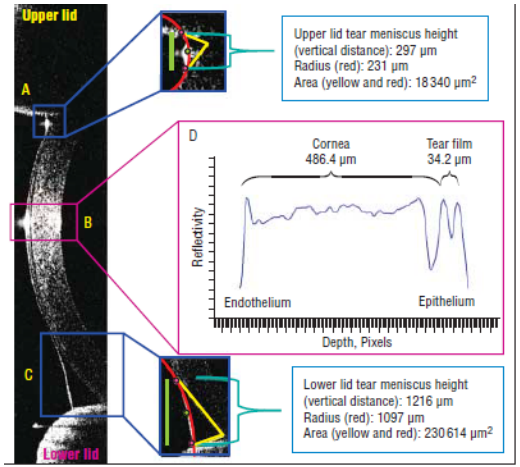
Five formulations with the desired globule sizes and viscosities were manufactured.

- **External collaboration with Absorption Systems (IDIQ 75F40119D10024)**

Optical coherence tomography to measure tear film and tear film menisci thickness in rabbits.

  - Instillation of cyclosporine ophthalmic emulsion
  - Already have human data from Wang et al. (2008)

Model validation of previously developed rabbit model



Tear Film Thickness and Tear Meniscus Measurement Wang et al, Arch Ophthalmol, 126, 619 (2008)

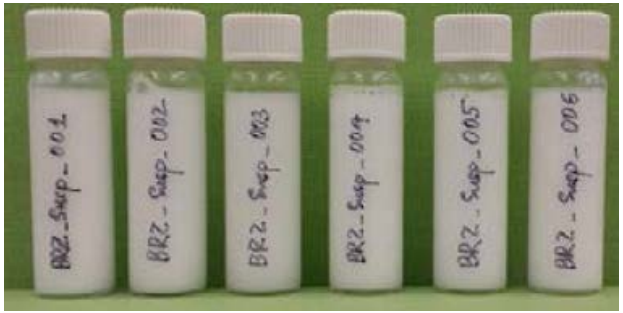
Ocular PBPK-PD Model Development

***Purpose**: to relate the ophthalmic suspension formulation changes to PD effect*

- **Internal collaboration with OTR:**

Six formulations prepared with the desired particle sizes and viscosities.

PSD, rheology, polymorphism, interfacial tension and interfacial rheology, pH, osmolality, assay, and drop weight were characterized



- **External collaboration with Absorption Systems (IDIQ 75F40119D10024)**

Products to be tested

Task Order	Pharmacological Class	API and concentration	Trade Name	Dosage form	NDA	Sponsor	Approval
2a	Placebo						
	Topical carbonic anhydrase inhibitors	Brinzolamide 1%	AZOPT®	Suspension	N020816	Novartis	April 1, 1998
		Brinzolamide 1%	--	Suspension	FDA's in-house formulation		
		Dorzolamide hydrochloride (EQ 2% Base)	TRUSOPT®	Solution	N020408	Merck	Dec 9, 1994
2b	Topical carbonic anhydrase inhibitor and/or Alpha-2 agonist or beta blockers (beta-adrenergic)	Brimonidine tartrate 0.2%	ALPHAGAN® (Discontinued, Generic available)	Solution	N020613	Allergan	Sep 6, 1996
		Brimonidine tartrate 0.2% + Brinzolamide 1%	SIMBRINZA™	Suspension	N204251	Novartis	Apr 19, 2013
		Betaxolol 0.25%	BETOPTIC®	Suspension	N019845	Novartis	Dec 29, 1989

Ocular PBPK-PD Model Development

***Purpose**: to relate the ophthalmic suspension formulation changes to PD effect*

- **External collaboration with Absorption Systems (IDIQ 75F40119D10024)**

PK/PD measurement

- Placebo
- RLD
- FDA formulations

Group	N	Treatment (OU)	Dose Route (OU)	Dose Volume (µL/eye)	Collection Time Points	Tissues Collected	IOP
0	6	Placebo	Topical Ophthalmic Frequency QD	≤50	Not required	Not required	0.25, 0.5, 1, 2, 4, and 8 hours post dose
1	6	Drug product		≤50	1, 3, 5, 10, 20, 30, 60, & 120 minutes post dose*	Tears	0.25, 0.5, 1, 2, 4, and 8 hours post dose
2	12	Drug product		≤50	0.25, 0.5, 1, 2, 4, and 8 hours post dose**	AH, Cornea, Conjunctiva, ICB, Lens, Sclera, Choroid, Retina. Plasma	0.25, 0.5, 1, 2, 4, and 8 hours post dose

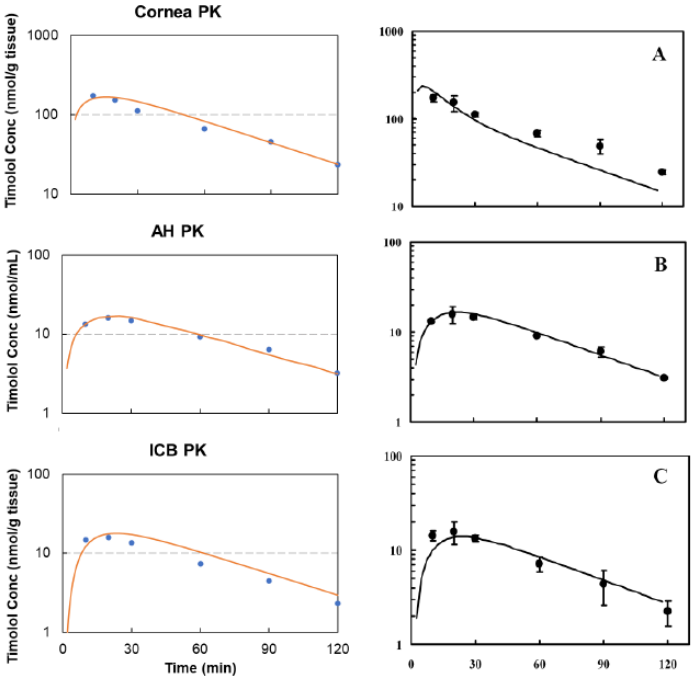
Single dose

Group	N	Treatment (OU)	Dose Route (OU)	Dose Volume (µL/eye)	Collection Time Points	Tissues Collected	IOP
1	X	Drug product	Topical Ophthalmic Frequency BID for 14 days	≤50	Day 1,7 and Day 14: 0.25, 0.5, 1, 2, 4, and 8 hours post dose	AH, Cornea, Conjunctiva, ICB, Lens, Sclera, Choroid, Retina. Plasma	Every alternate day 0.25, 0.5, 1, 2, 4, and 8 hours post dose

Multiple-dose

Timolol Rabbit PD models

PK model



Durairaj PD model

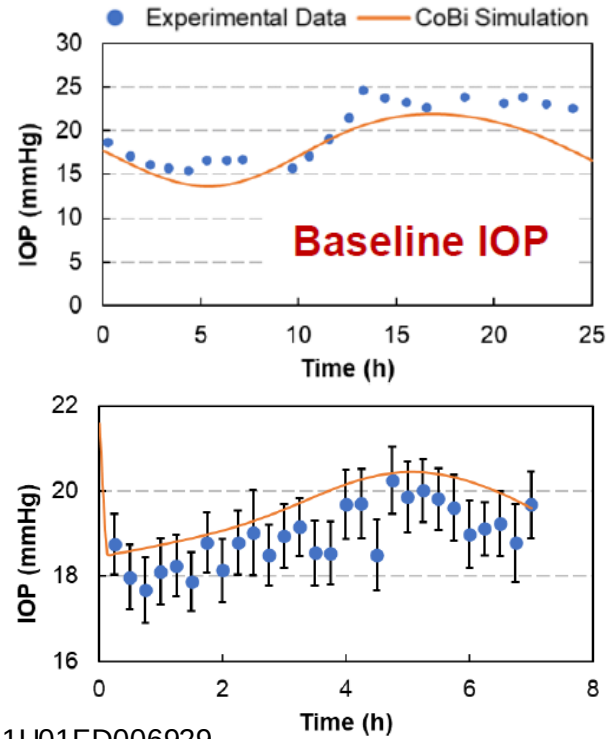


Figure courtesy of CFD RC, 1U01FD006929

Translation from Preclinical to Human

- Determine likely changes in ocular physiology between rabbit and human
- Extrapolate rabbit models to human models
- Validate the extrapolated human models

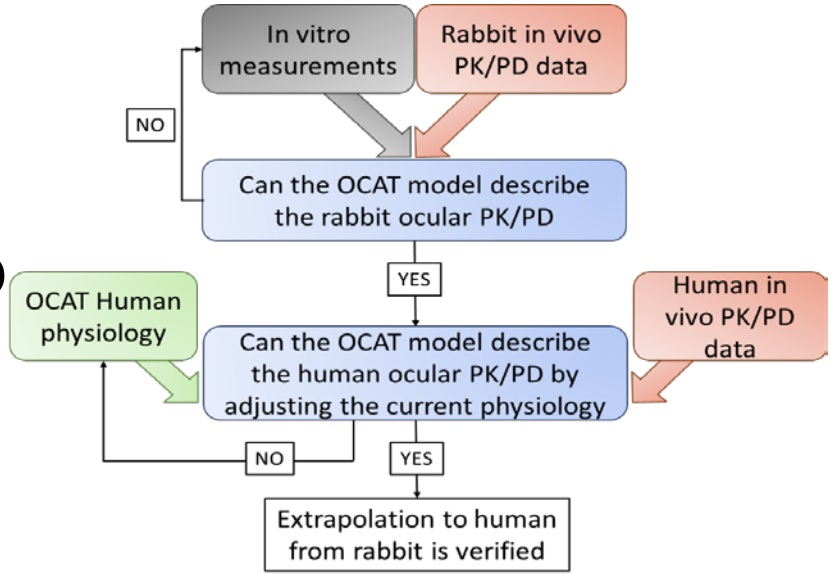


Figure courtesy of Simulations Plus, 1U01FD006927

Challenges in Ophthalmic Modeling

- Lack of direct eye tissue concentrations for model validation
- Lack of information on melanin binding in eye tissues
- Lack of information on metabolizing enzyme levels in eye tissues
- Mainly considering passive permeation through eye tissue barriers, not active transport

Future Directions

- Model extrapolations to human from preclinical species
- Incorporation of metabolizing enzyme and transport proteins in eye models
- PD model development and validation for IOP drugs
- High quality in vitro studies for IVIVE/C modeling

Challenge Question #1

For topical ophthalmic drug products, FDA has approved generics of the branded name products with all the dosage forms, except

A. Suspensions

B. Emulsions

C. Ointments

D. Solutions

Challenge Question #2

For topical ophthalmic generics, which of the following options is NOT often directly used to demonstrate BE?

A. In vitro studies.

B. In vivo local eye tissue PK studies.

C. In vivo systemic PK studies

D. Comparative clinical endpoint studies

Summary

- Demonstrating BE for ophthalmic products may be challenging
- PBPK model can integrate physiology, drug/drug product properties, existing in vitro and in vivo data
- PBPK modeling may bridge the knowledge gap in ophthalmic generic development and assessment
- PBPK modeling approaches may be utilized in regulatory submissions for generic drugs

Acknowledgements

- FDA/CDER/OGD/ORS
  - Andrew Babiskin
  - Ross Walenga
  - Lanyan (Lucy) Fang
  - Liang Zhao
  - Yan Wang
  - Darby Kozak
  - Lei Zhang
  - Robert Lionberger
- FDA/CDER/OPQ/OTR
  - Xiaoming Xu
- External grantees and contractors
  - HHSF223201810255P, Simulations Plus, PI: Jessica Spires
  - HHSF223201810151C, CFD RC, PI: Andrzej Przekwas
  - 1U01FD006927, Simulations Plus, PI: Jessica Spires
  - 1U01FD006929, CFD RC, PI: Carrie German
  - IDIQ 75F40119D10024, Absorption Systems, POC: Vatsala Naageshwaran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