Advancing current PBPK model applications to support internal development and regulatory decisions

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EUFEMED

Workshop 1: Modeling and simulations, including PBPK to improve the clinical development

May 15th 2019

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Take home messages:

- Number of applications received by the U.S. FDA including PBPK models is exponentially rising since 2008
- The U.S. FDA is an advocate of the PBPK approach to waive some clinical trials
- The U.S. FDA is investing time and money to improve the confidence level for PBPK model

Outline:

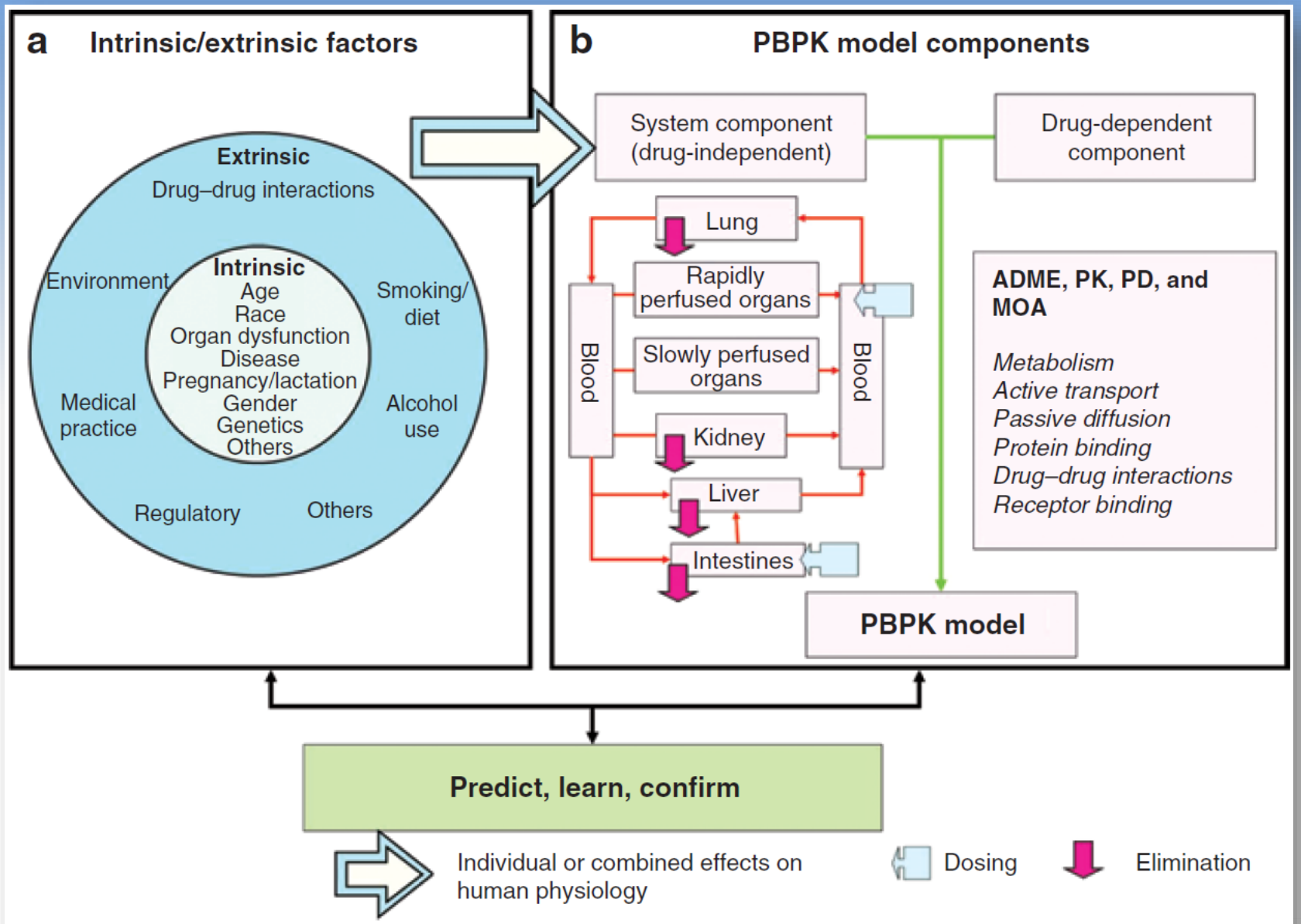
- U.S. FDA's definition of PBPK
- PBPK and the U.S. FDA, a few numbers…
- U.S. FDA's efforts to improve the science supporting PBPK models development
- Case study: *How can PBPK modeling be used to accelerate the development of ophthalmic generic drugs?*

PBPK model: The U.S. FDA's definition

The U.S. Food and Drug Administration (U.S. FDA) describes a Physiologically-Based Pharmacokinetic (PBPK) analysis such as models and simulations that **combine physiology, population, and drug characteristics to mechanistically describe the PK and/or pharmacodynamic (PD) behaviors of a drug**.

Throughout a drug's life cycle, PBPK model predictions can be used to support decisions on whether, when, and how to conduct certain clinical pharmacology studies, and to support dosing recommendations in product labeling (U.S. FDA, PBPK analysis, Guidance for industry).

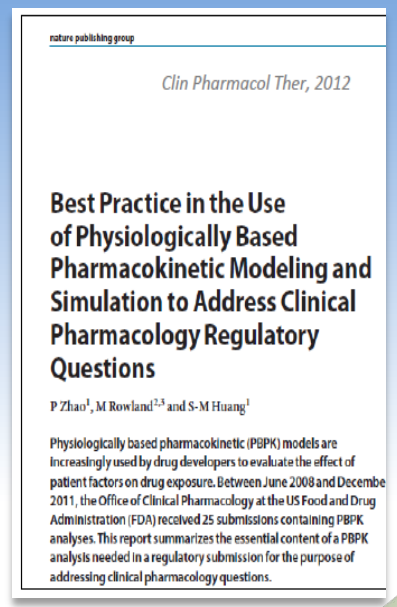
PBPK model: The U.S. FDA's definition



The degree of complexity of the PBPK model can vary according to the need.

Adapted from: Zhao 2011

PBPK and the U.S. FDA, a few numbers… guidelines


nature publishing group

Clin Pharmacol Ther, 2012

Best Practice in the Use of Physiologically Based Pharmacokinetic Modeling and Simulation to Address Clinical Pharmacology Regulatory Questions

P Zhao[1], M Rowland[2,3] and S-M Huang[1]

Physiologically based pharmacokinetic (PBPK) models are increasingly used by drug developers to evaluate the effect of patient factors on drug exposure. Between June 2008 and Decembe 2011, the Office of Clinical Pharmacology at the US Food and Drug Administration (FDA) received 25 submissions containing PBPK analyses. This report summarizes the essential content of a PBPK analysis needed in a regulatory submission for the purpose of addressing clinical pharmacology questions.

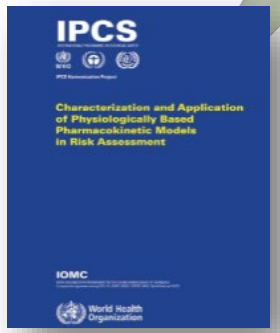
2010
WHO
guidance

2012
Opinion
paper from
FDA

2014
FDA & EMEA
workshops

2016
FDA & EMEA
Draft guidance

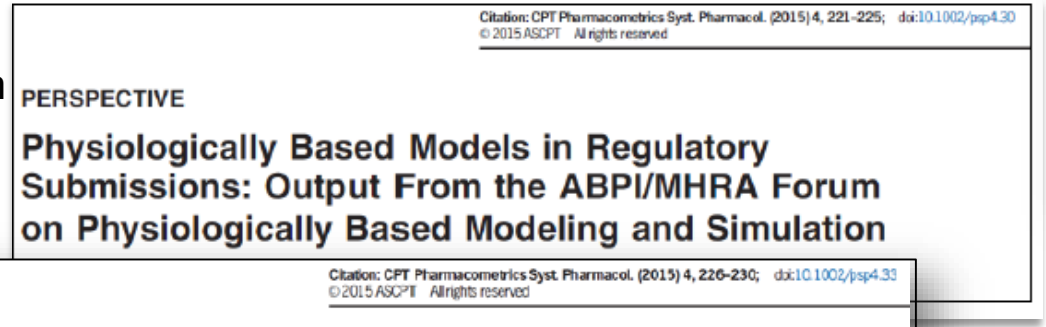
2018
FDA final
guidance


IPCS

Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment

IOMC

World Health Organization


Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 4, 221–225; doi:10.1002/psp4.30
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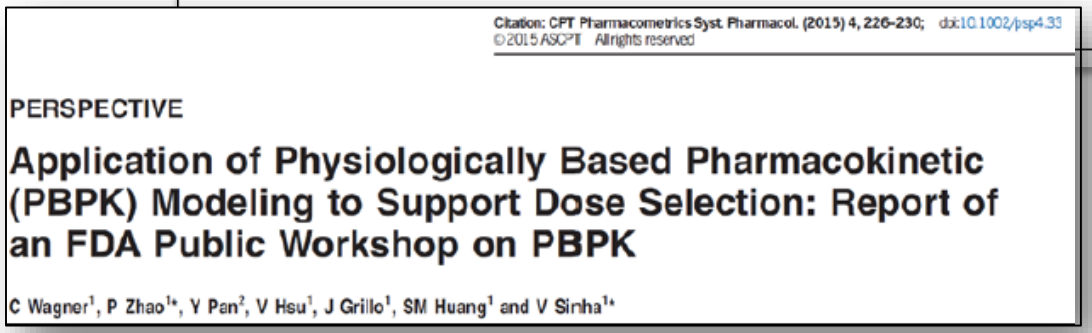
PERSPECTIVE

Physiologically Based Models in Regulatory Submissions: Output From the ABPI/MHRA Forum on Physiologically Based Modeling and Simulation


Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 4, 226–230; doi:10.1002/psp4.33
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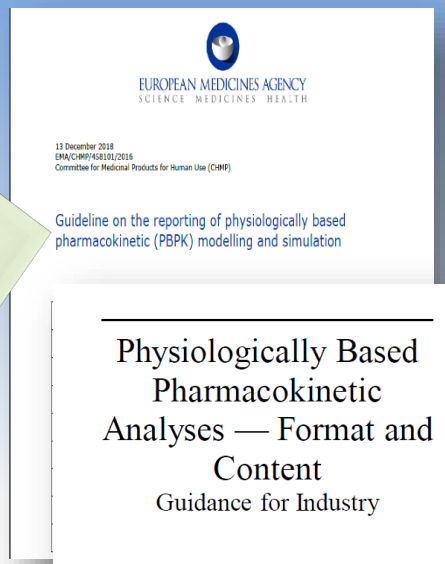
PERSPECTIVE

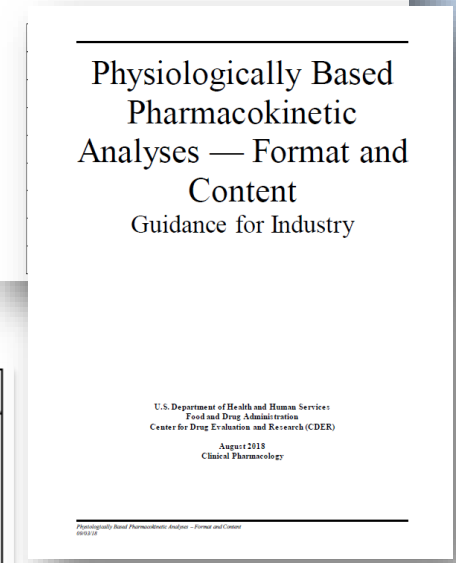
Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK

C Wagner[1], P Zhao[1]*, Y Pan[2], V Hsu[1], J Grillo[1], SM Huang[1] and V Sinha[1]*


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation


Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2018
Clinical Pharmacology

To be continued…

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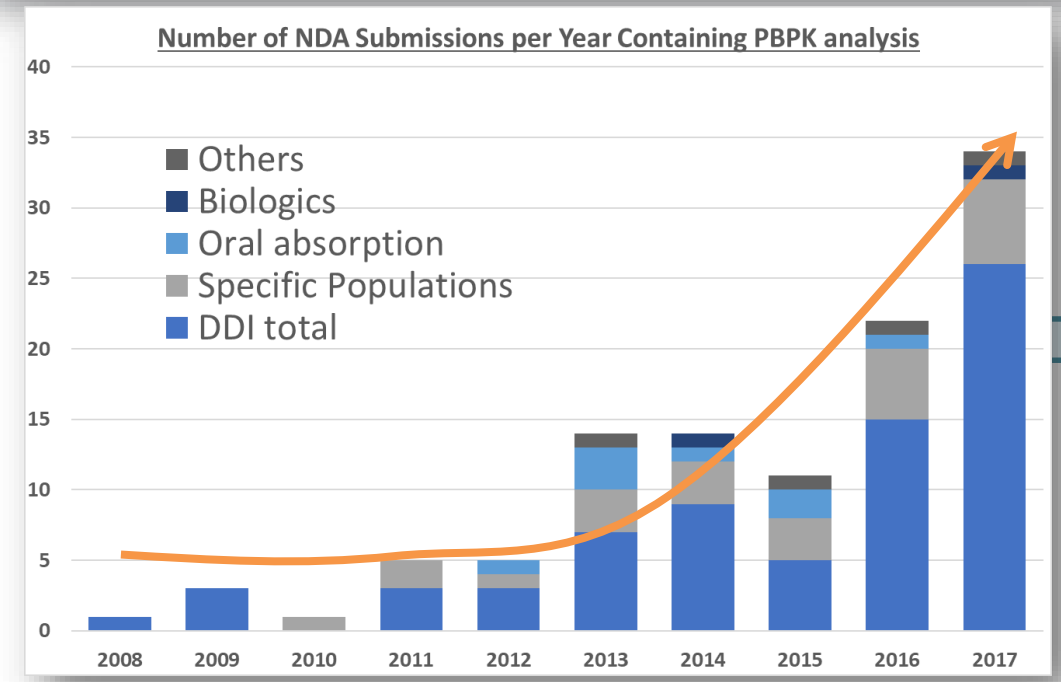
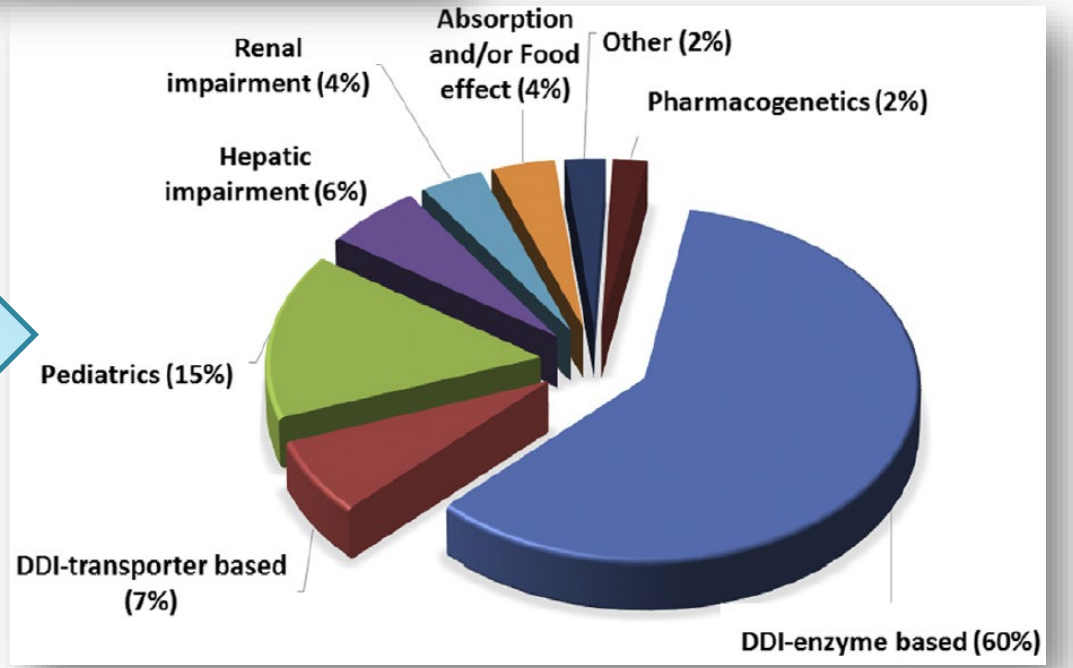
PBPK and the U.S. FDA, a few numbers… new drug application

Physiologically Based Pharmacokinetic Modeling in Regulatory Science: An Update From the U.S. Food and Drug Administration's Office of Clinical Pharmacology

Manuela Grimstein, Yuching Yang*, Xinyuan Zhang*, Joseph Grillo, Shiew-Mei Huang, Issam Zineh, Yaning Wang

Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland 20993





Adapted from: Grimstein 2018

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PBPK and the U.S. FDA, a few numbers…generic drugs

Data from 2016:

Type	No.	Examples
ANDA Reviews & Citizen petitions	22	❖ Implement clinical relevant PK metrics for BE assessment
Pre-ANDA interactions (including CC)	26	❖ Development of BE criteria for analgesics ❖ Assessment of BE standards for GI locally acting products ❖ Simulation of in vivo alcohol dose dumping studies
BE Guidances	31	❖ Simulations for the development of BE criteria for HVDs and NTI drugs
Regulatory Research Studies	30	❖ Pharmacokinetic(PK)/Pharmacodynamic (PD) modeling and simulation to determine the appropriate study design and evaluate clinical endpoint sensitivity for BE assessment

ANDA: abbreviated new drug application; BE: bioequivalence: CP: citizen petition; CC: controlled correspondence; GI: gastrointestinal; HVD: highly variable drugs; NTI: narrow therapeutic index.

https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM550577.pdf

PBPK and the U.S. FDA, a few numbers…acceptance

Physiologically Based Pharmacokinetic Model Qualification and Reporting Procedures for Regulatory Submissions: A Consortium Perspective

Mohamad Shebley[1], Punam Sandhu[2], Arian Emami Riedmaier[1], Masoud Jamei[3], Rangaraj
Aarti Patel[5], Sheila Annie Peters[6], Venkatesh Pilla Reddy[7], Ming Zheng[8], Loeckie de Zwar
Maud Beneton[10], Francois Bouzom[11], Jun Chen[12], Yuan Chen[13], Yumi Cleary[14], Christian
Gemma L. Dickinson[16], Nassim Djebli[12], Heidi J. Einolf[17], Iain Gardner[3], Felix Huth[18], F
Feras Khalil[19], Jing Lin[20], Aleksandrs Odinecs[21], Chirag Patel[22], Haojing Rong[23], Edgar Sc
Pradeep Sharma[7], Shu-Pei Wu[25], Yang Xu[26], Shinji Yamazaki[27], Kenta Yoshida[13] and Mal

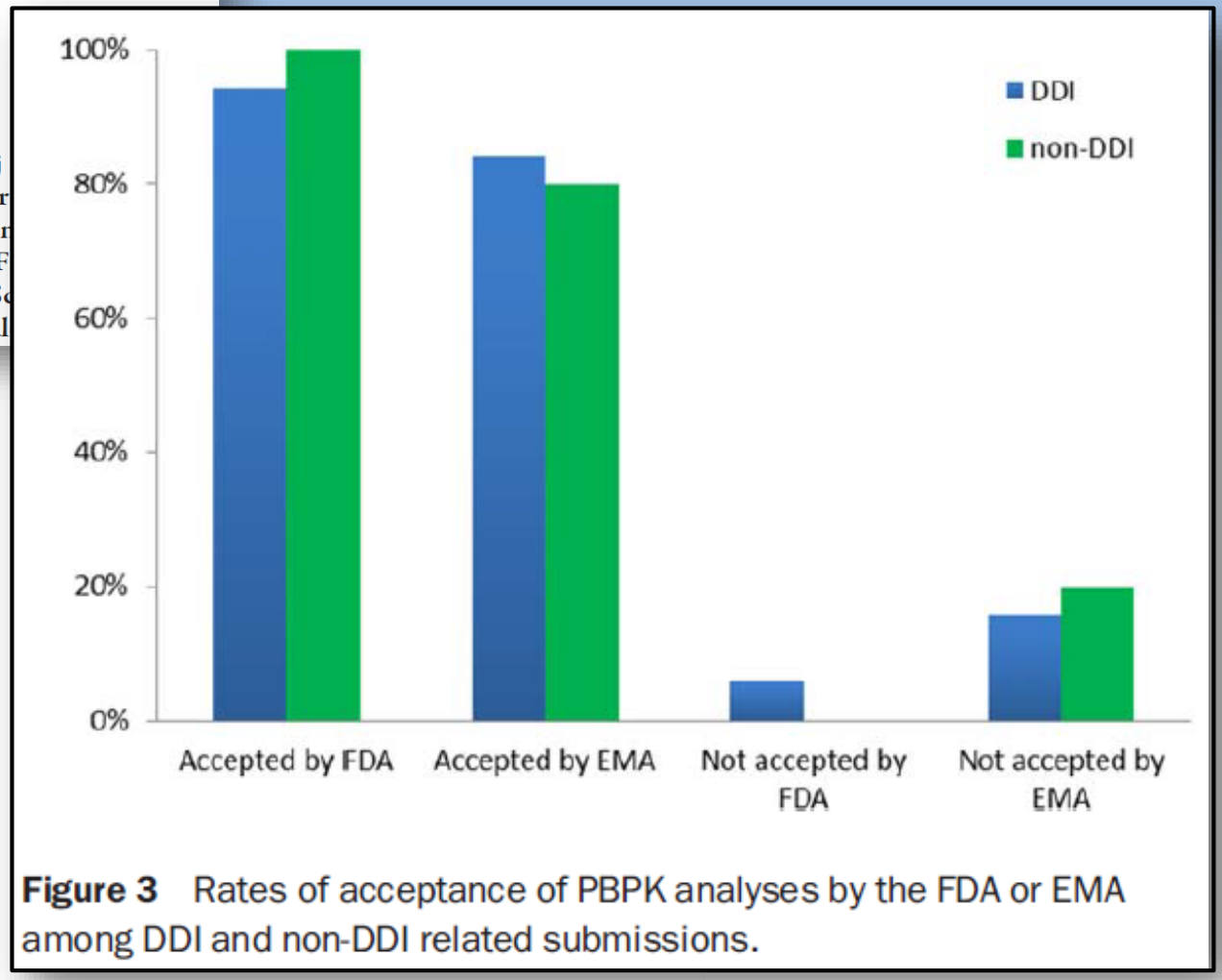

Figure 3 Rates of acceptance of PBPK analyses by the FDA or EMA among DDI and non-DDI related submissions.

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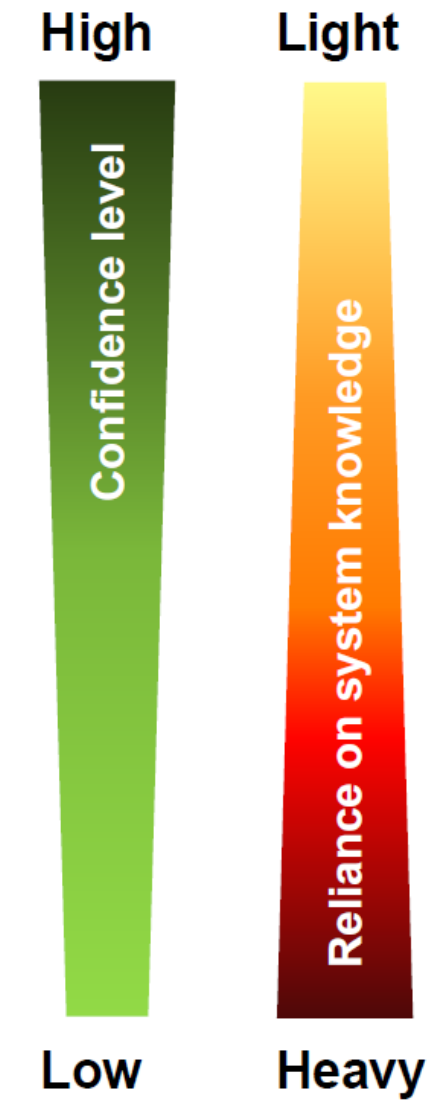
PBPK and the U.S. FDA, a few numbers…acceptance

	Applications	Status
Drug-drug Interactions	*Drug as enzyme substrate*	• *Substrate/inhibitor models verified with key clinical data can be used to simulate untested scenarios and support labeling*
	Drug as enzyme perpetrator	• *Use to confirm the lack of enzyme inhibition* • *Additional evidence needed to confirm predictive performance for positive interactions*
	Transporter-based	• *In vitro-in vivo extrapolation not mature* • *Complicated by transporter-enzyme interplay* • *Predictive performance yet to be demonstrated*
Specific populations	*Organ impairments (hepatic and renal)*	• *Predictive performance yet to be improved* • *System component needs an update*
	Pediatrics	• *Allometry is reasonable for PK down to 2 years old* • *Less than 2 years old ontogeny and maturation need to be considered*
Others with limited experience	*Pregnancy, ethnicity, geriatrics, obesity, disease states* *Food effect, formulation change, PH effect (including DDIs on gastric PH)* *Tissue concentration, drug delivery for locally-acting products*	

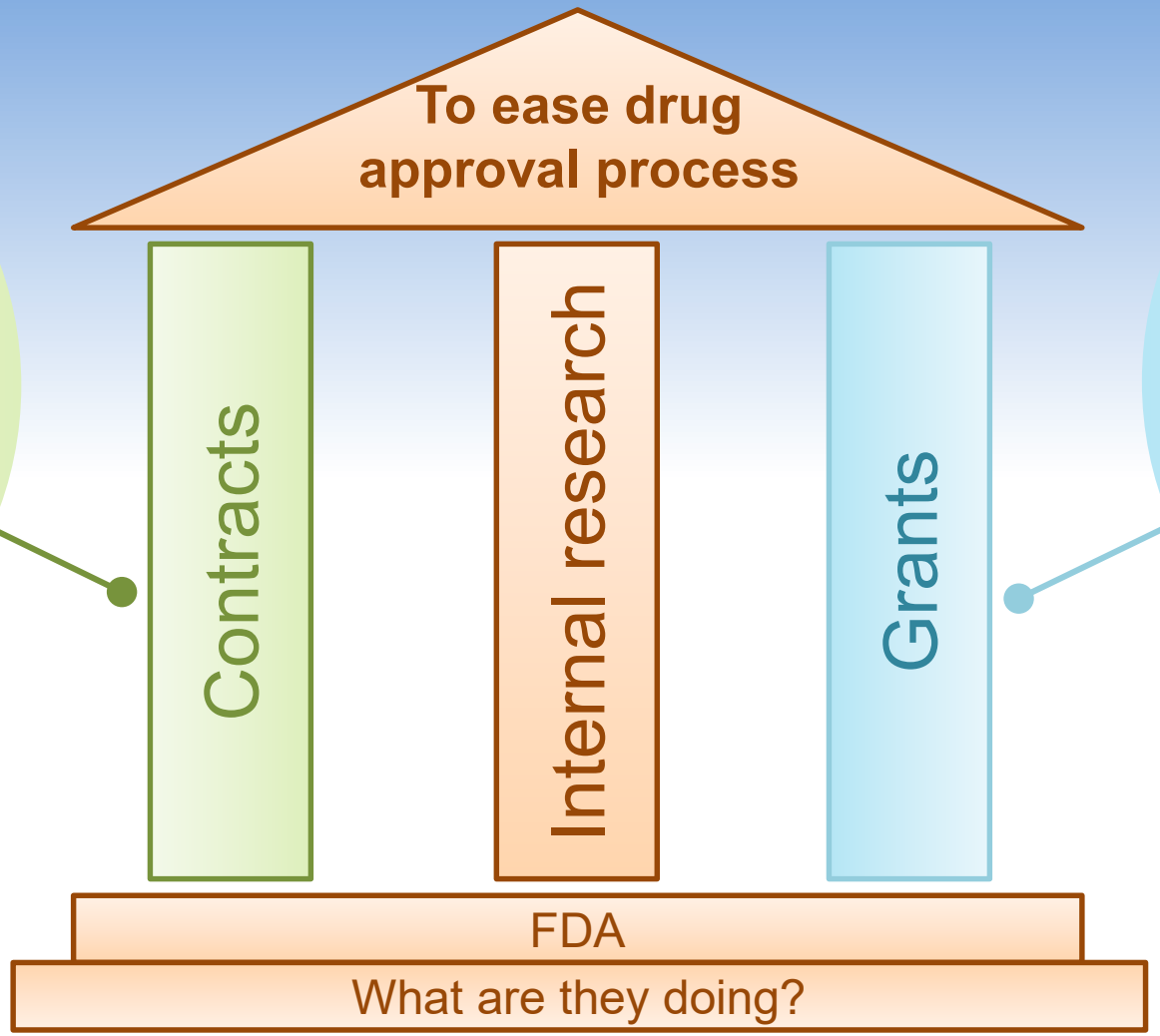
Updated from Wagner, CPT-PSP, 2015



https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM550577.pdf

U.S. FDA's efforts

- Purpose: To directly benefit the Federal Agency duties
- Scope: Defined by the Federal Agency
- Results: For Federal Agency



- Purpose: Advance public knowledge
- Scope: Defined by the recipient
- Results: For public

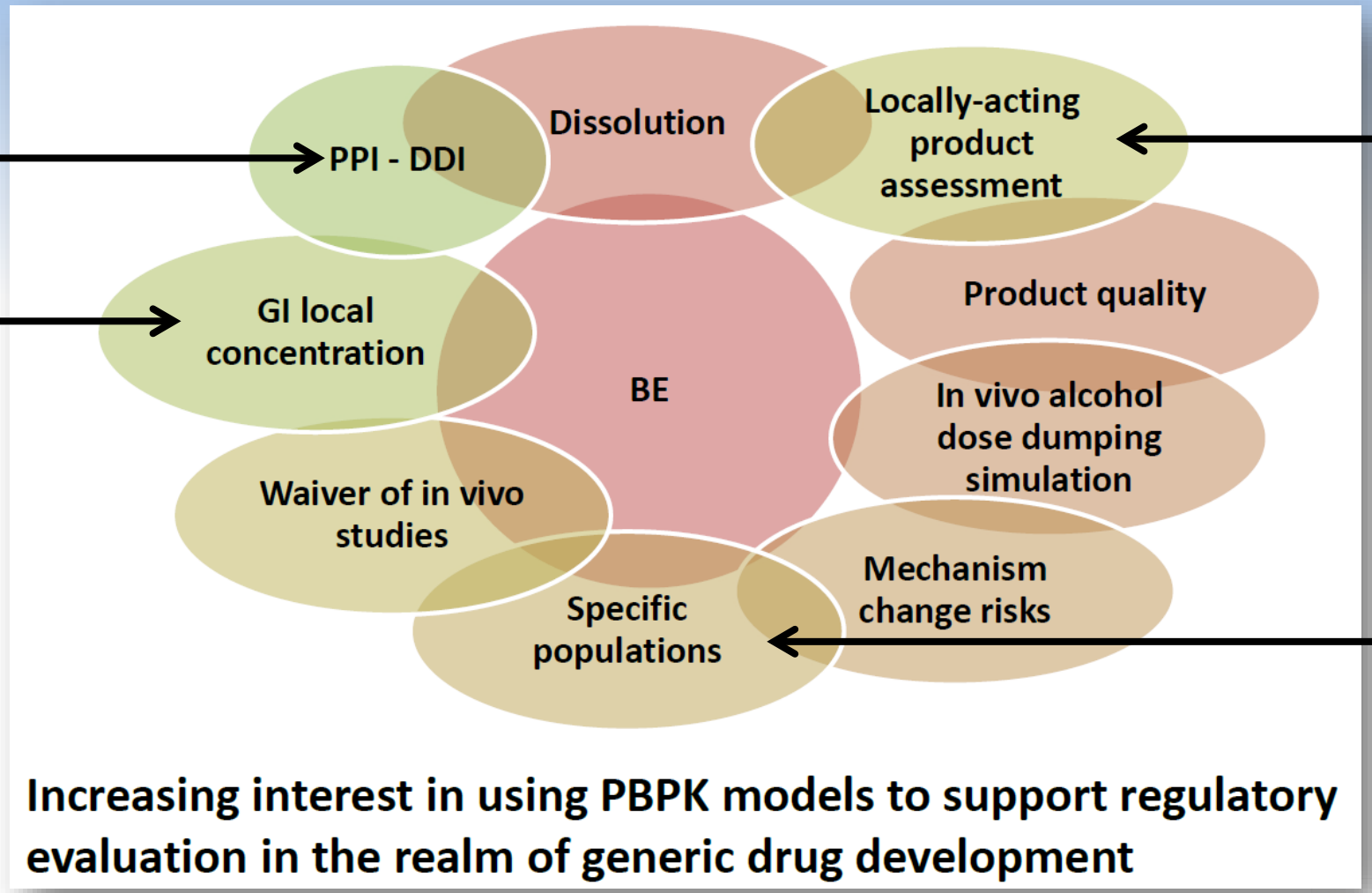
U.S. FDA's efforts

→ fill the knowledge gaps: science "black boxes"

→ Invest where the private sector will not

PBPK for:
pH modification
impact

PBPK for:
Prediction of
local GI
concentration
based on
plasma
concentration



PBPK for:
- Pulmonary
- Ocular
- Dermal

PBPK for:
Women GI
physiology
impact on BE
evaluation

Increasing interest in using PBPK models to support regulatory evaluation in the realm of generic drug development

https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM550577.pdf

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

Challenges:

- *Almost* all ophthalmic drug products (if not a solution,) have no generic available in the US market
- Prices of these drugs are very high in the US → It is a necessity for the FDA to approve generic drugs to reduce the cost for the US population and improve the number of patient being cured.

- However, bioequivalence (BE) clinical trials are extremely expensive for these kind of products due to the difficulty to sample in the BioPhase (aqueous humor).
- Therefore, these clinical trials usually have:
  - Number of subjects: usually above 1000
  - Parallel design
  - High variably
  - A significant chance to fail?

- New approach for BE evaluation is necessary → Model-informed drug development: PBPK
- In 2014, Simulations Plus was selected by the FDA to develop a PBPK model able to describe the PK of a drug following ocular administration
- FDA also performed internal research generating some in-house pre-clinical data to support model development

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

A sensitive UPLC-APCI-MS/MS method for determination of dexamethasone and its application in an ocular tissue distribution study in rabbits following topical administration

Murali K Matta,

Ashok Chockalin

Protocol for evaluation of topical ophthalmic drug products in different compartments of fresh eye tissues in a rabbit model

Ashok Chockalingam[1], Lin Xu[1], Sharron Stewart[1], Maxime LeMerdy[2], Eleftheria Tsakalozou[2] Jianghong Fan[2], Vikram Patel[1] and Rodney Rouse[1]*

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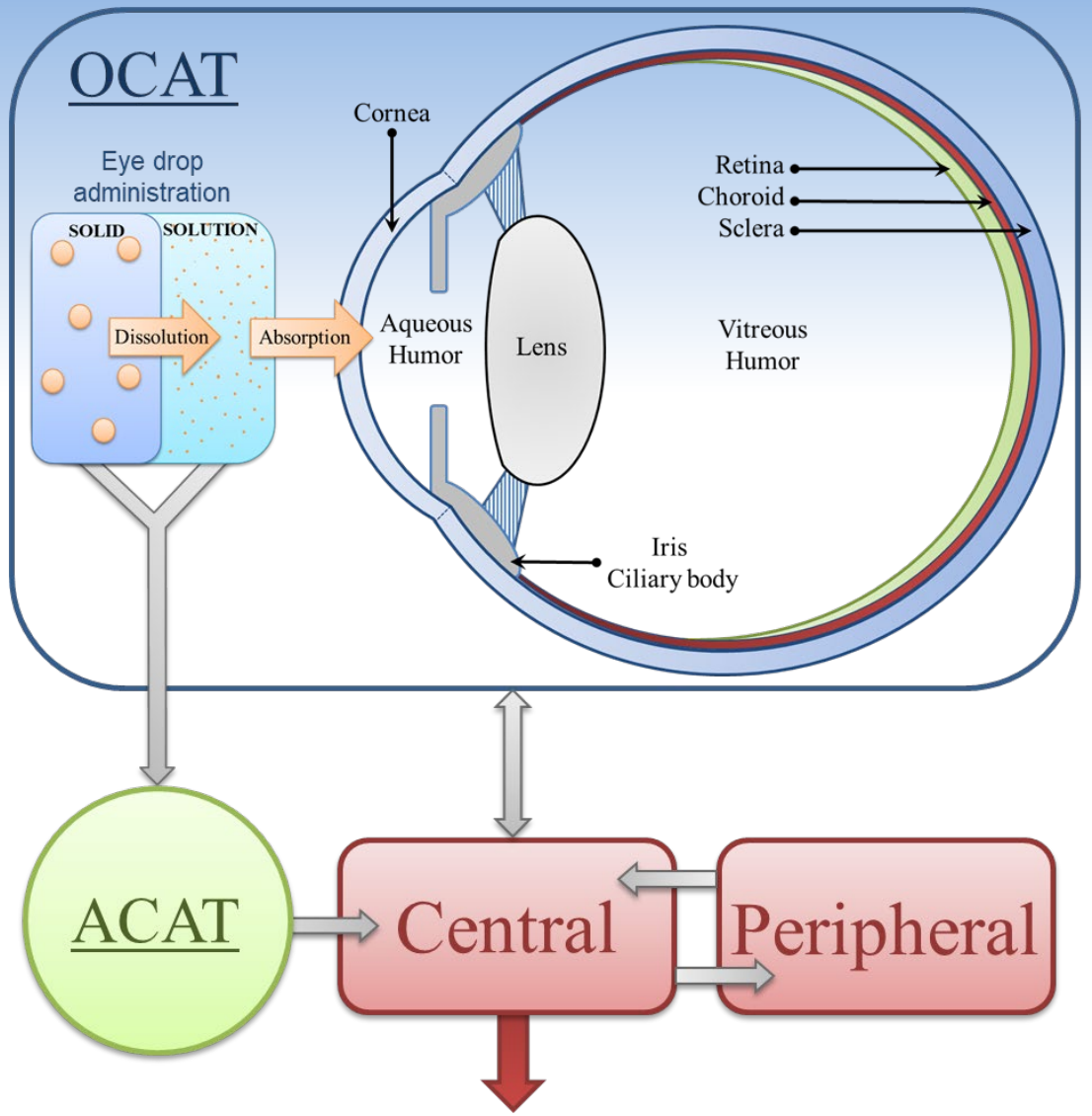
[1]Office of T
Science

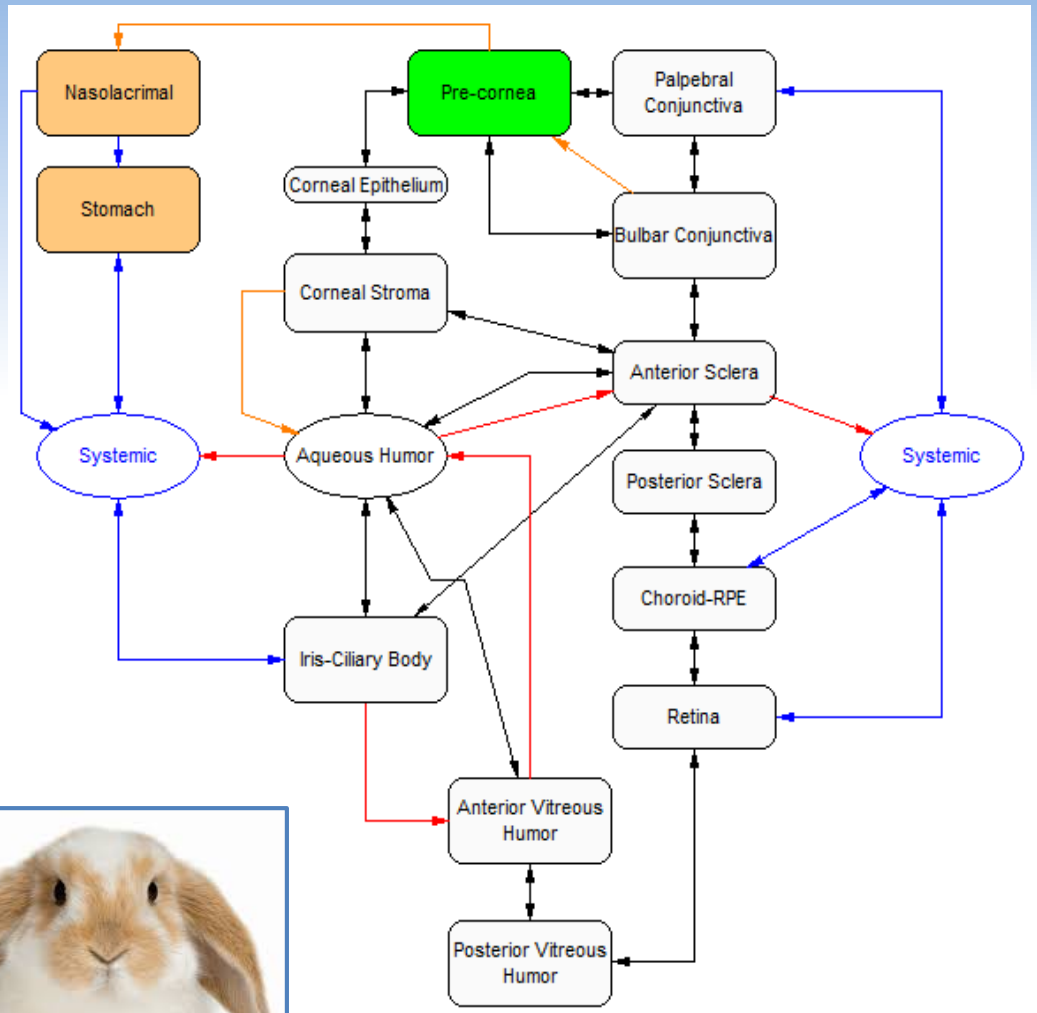
[2] Office of

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]

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





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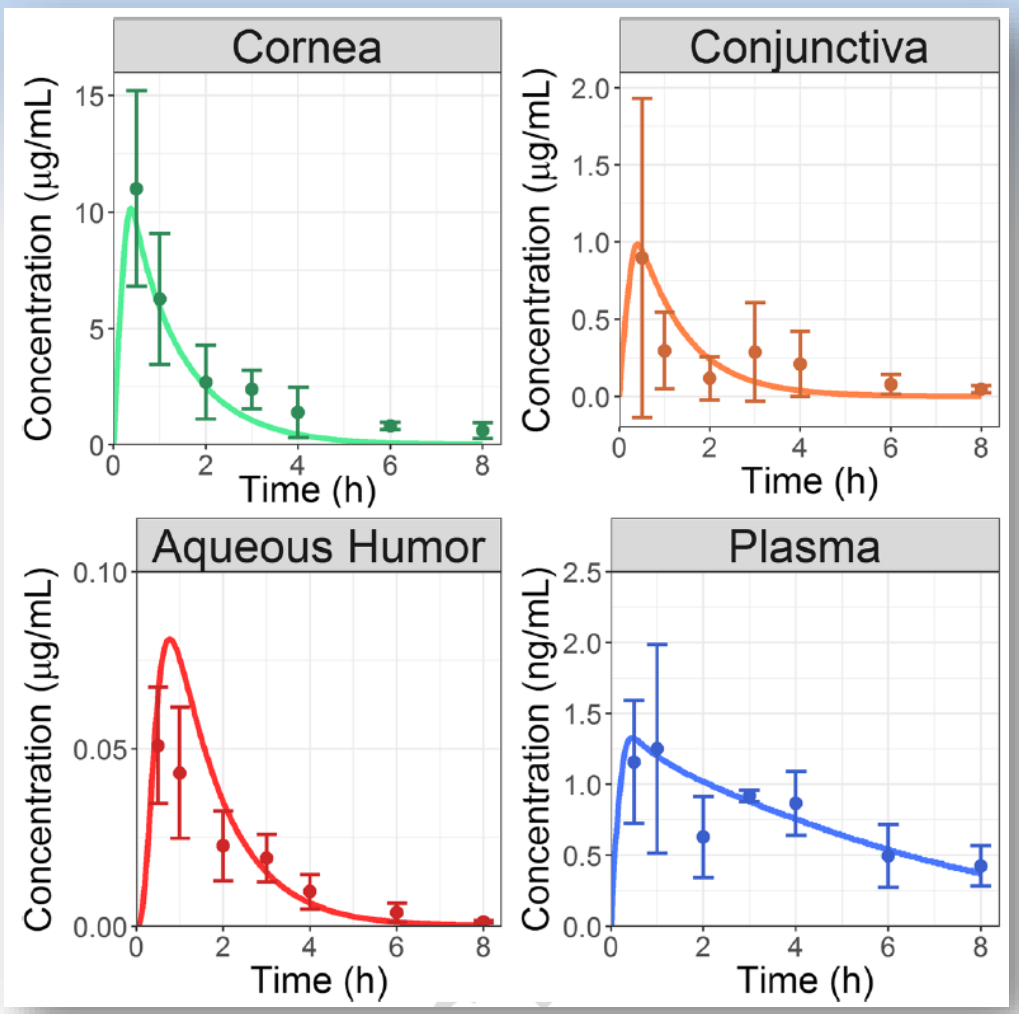
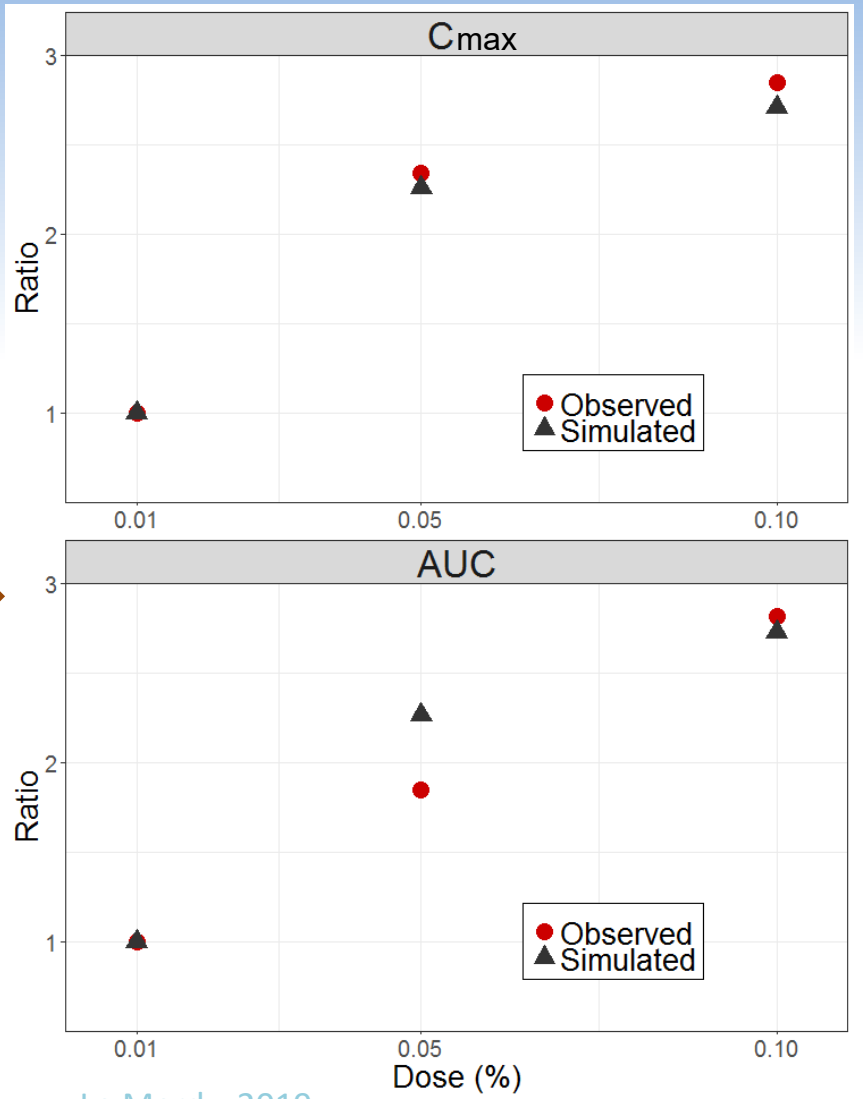
Case study: How can PBPK modeling be used to accelerate the development of ophthalmic generic drugs?

During model development, it was verified against data from literature following the administration of multiple drugs as ophthalmic solution and suspension.

Model development for dexamethasone 0,05%:



Validation 1: Dose

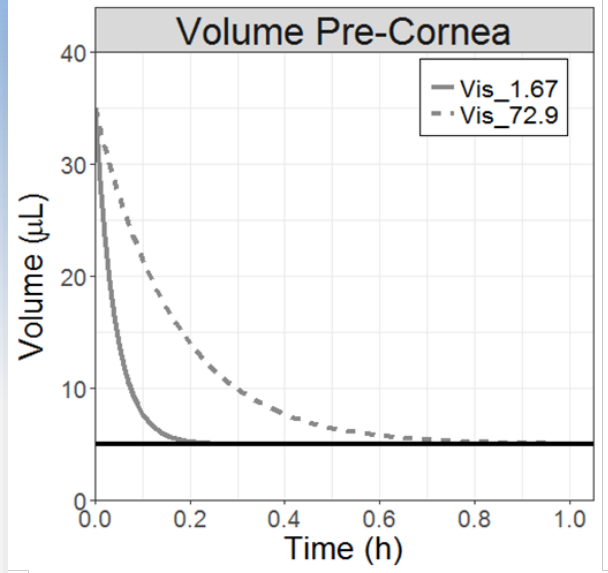


Le Merdy, 2019

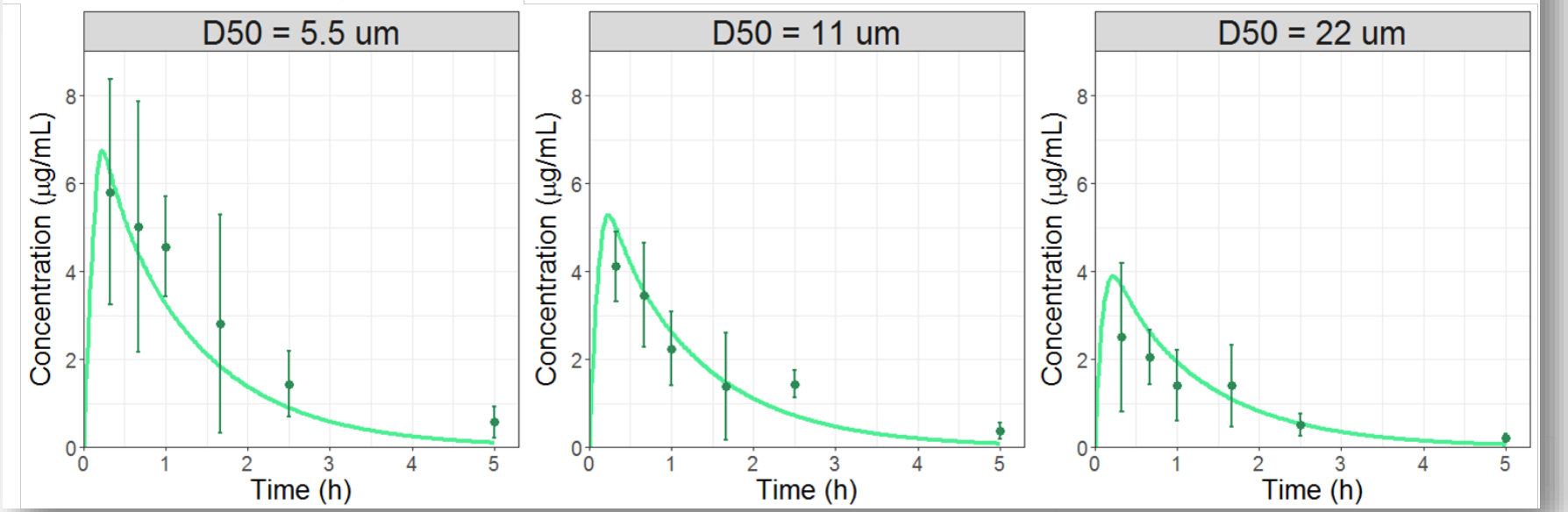
Case study: How can PBPK modeling be used to accelerate the development of ophthalmic generic drugs?

Validation 2: Viscosity

Validation 3: PS

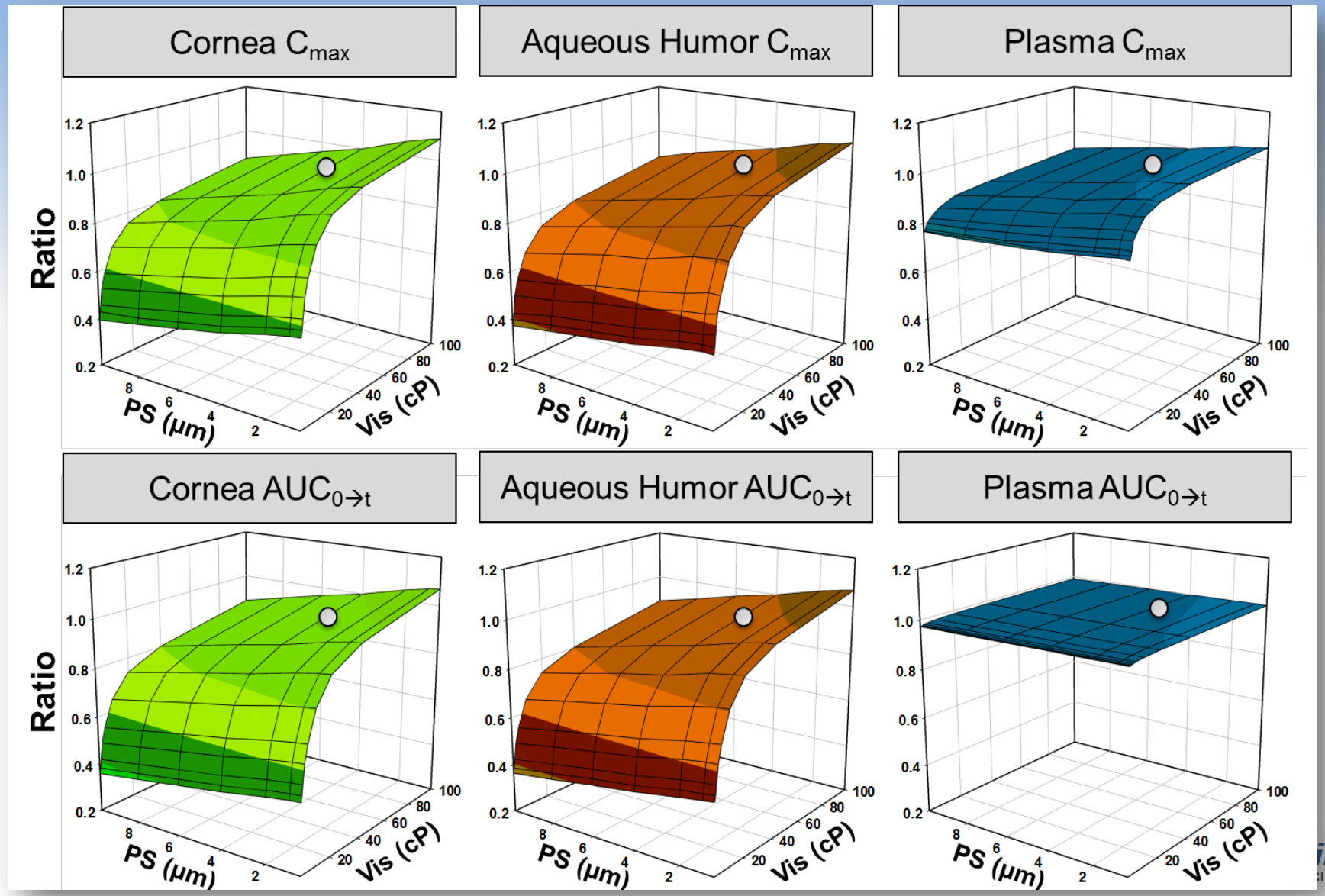


	C_{max} (µg/mL)		$AUC_{0\rightarrow3}$ (µg.h/mL)	
	Observed	Simulated	Observed	Simulated
TOBRADEX ST© 0.05%	0.106 ± 0.019	0.081	0.191 ± 0.01	0.13
TOBRADEX© 0.1%	0.069 ± 0.022	0.06	0.118± 0.006	0.095



Le Merdy, 2019

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



Le Merdy, 2019

Physiologically-based Pharmacokinetic Model to Support Ophthalmic Suspension Product Development

Maxime Le Merdy*, Jianghong Fan, Andrew Babiskin, Liang Zhao CONTACT INFORMATION: Andrew.Babiskin@fda.hhs.gov

Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD, USA

OBJECTIVES

To use a rabbit ocular physiologically-based pharmacokinetic (PBPK) model to compare a suspension to a solution for ophthalmic products

BACKGROUND

- Development of new therapeutics or generic drugs for ocular disease is a challenging task due to the complexity of the ocular system.
- To optimize the therapeutic drug level reaching the biophase, multiple formulation strategies have been used to prolong the tear residence time of topical ophthalmic drug products by increasing the viscosity or enhancing the amount reaching the target site by dosage modification[1].
- For most ophthalmic suspension products, we calculate that 90% or more of the active ingredient remains undissolved.
- Previously, a dexamethasone (Dex) ocular PBPK model (OCAT module in GastroPlus™ V9.6, Simulations Plus, Inc.) was developed and verified in rabbit for Dex suspension formulations with differences in particle size, strength, and viscosity (manuscript submitted[2]).

METHODS

- Using the verified OCAT-PBPK model, the following simulations (S1-S11) were performed:

	Suspension Dose (%)	Solution amount (µg)	Solid amount (µg)	Particle clearance mechanism	DR (min^{-1})
Suspended particles clearance process from the ocular surface					
S1	0.1	2.67	27.33	DR + TFR	1
S2	0.1	2.67	27.33	DR	1
S3	0.1	2.67	27.33	TFR	1
S4	0.1	2.67	27.33	-	1
Suspension advantages compare to a saturated solution					
S5	0.05	2.67	12.33	DR + TFR	0.1
S6	*	2.67	-	-	0.1
Dose increase for ophthalmic suspensions					
S7	0.01	2.67	0.33	DR + TFR	0.1
S8	0.05	2.67	12.33	DR + TFR	0.1
S9	0.1	2.67	27.33	DR + TFR	0.1
Dose-viscosity relationship					
S10	0.1	2.67	27.33	DR + TFR	0.4
S11	0.1	2.67	27.33	DR + TFR	0.1

Table 1: List of simulations performed in GastroPlus™ for rabbit to understand (1) the suspended particles clearance process from the ocular surface; (2) the advantages of suspension as compared to a saturated solution; (3) the impact of dose increase for ophthalmic suspensions; and (4) the relationship between dose and viscosity for ophthalmic suspensions.

DR = drainage rate
TFR = tear flow rate

- Viscosity of formulations are controlled by adjusting the DR

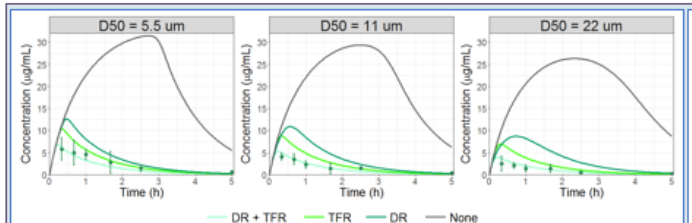


Figure 1: Observed Dex cornea concentrations following the administration of three formulations of Dex ophthalmic suspensions 1% to rabbit eye[3]. The formulations differ in median particle size (D50; 5.5, 11 and 22 µm) (green dots). Lines represent simulations for different elimination mechanisms from ocular surface.

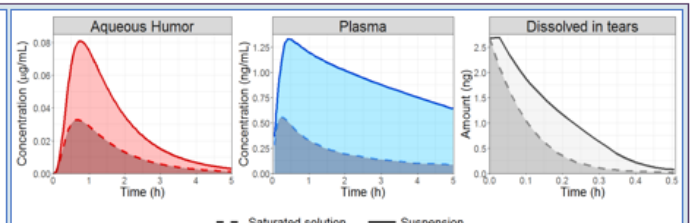


Figure 2: Dex concentration in aqueous humor and plasma and dissolved amount in tears following the administration of Dex suspension 0.05% (solid lines) or saturated solution (dashed lines).

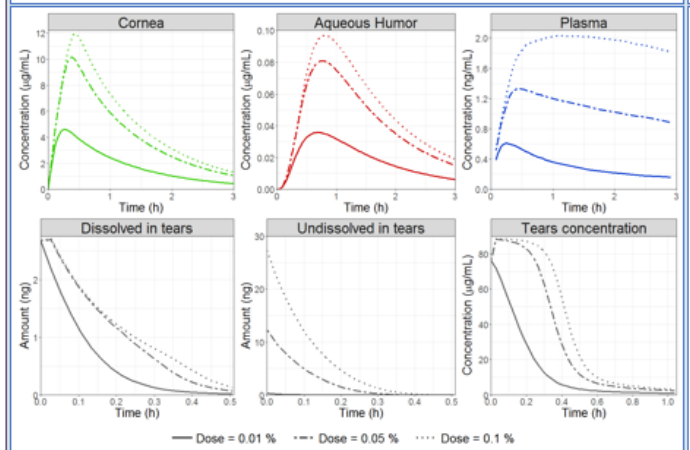


Figure 3: Dex cornea, aqueous humor, plasma and tears concentrations following the administration of 3 different strengths of Dex suspension: 0.01, 0.05, 0.1%. Dissolved and undissolved amount of Dex tears are also presented

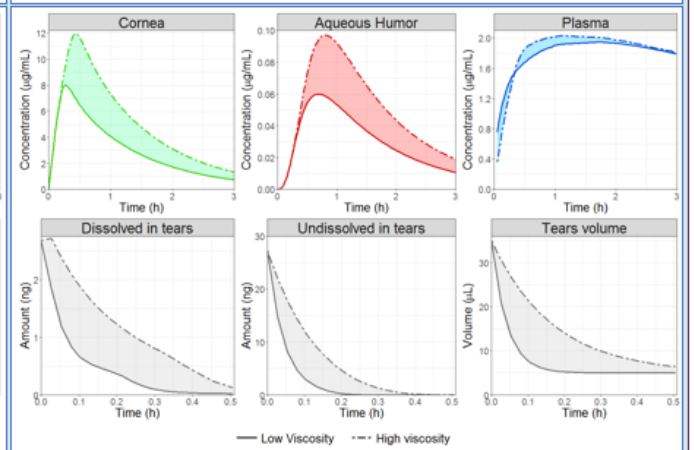


Figure 4: Dex cornea, aqueous humor and plasma concentrations, tears volumes, and dissolved and undissolved amounts of Dex in tears following the administration of Dex 0.1% suspensions with high or low viscosity (Table 1).

RESULTS/CONCLUSIONS

- Both DR and TFR are critical to adequate corneal predictions.
- Dex suspension 0.05% has a 2.5- and 5-fold higher aqueous humor and plasma AUC, respectively, compared to saturated solution.
- Strength increase by 5- or 10-fold induces a respective 2.2- or 3.3-fold increase in aqueous humor and 4.4- or 8.6-fold increase in plasma Cmax and AUC
- Increasing formulation viscosity (from 1.6 to 75 cP) causes an overall increase in Dex available for absorption in the cornea resulting in a higher ocular Cmax and AUC with no significant impact on systemic exposure.
- A model able to correlate formulation changes to both ocular and plasma exposure is a necessary tool to support ocular product development taking into consideration the pharmacodynamic and toxicology aspects.

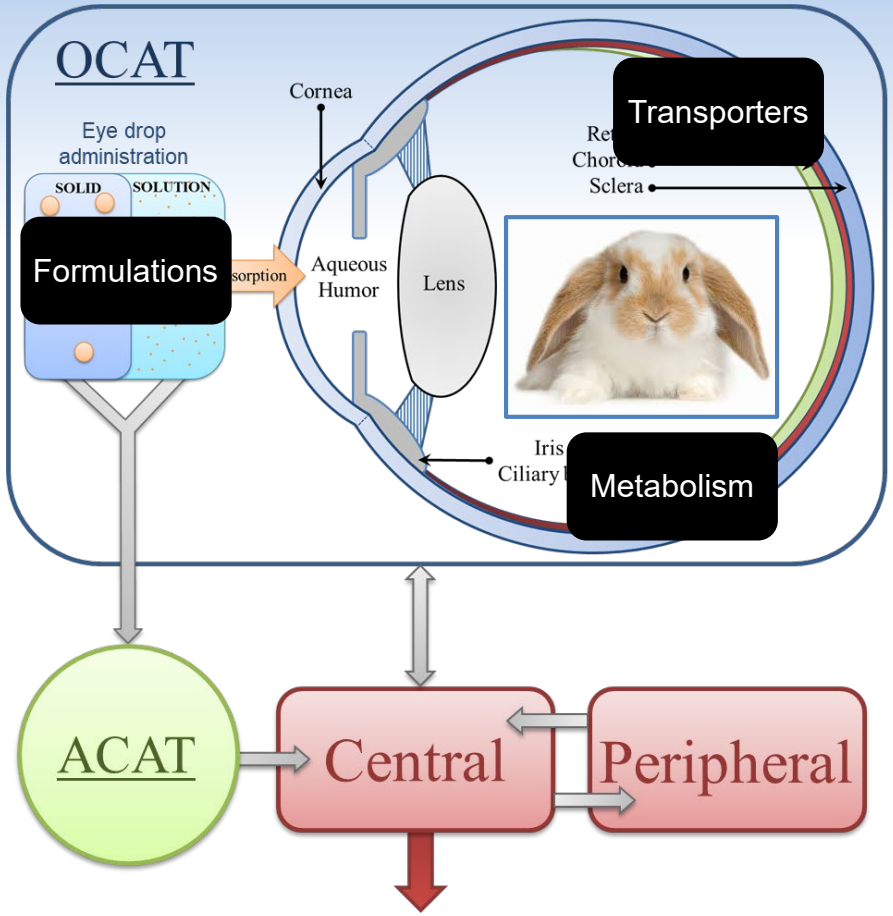
REFERENCES & FUNDING

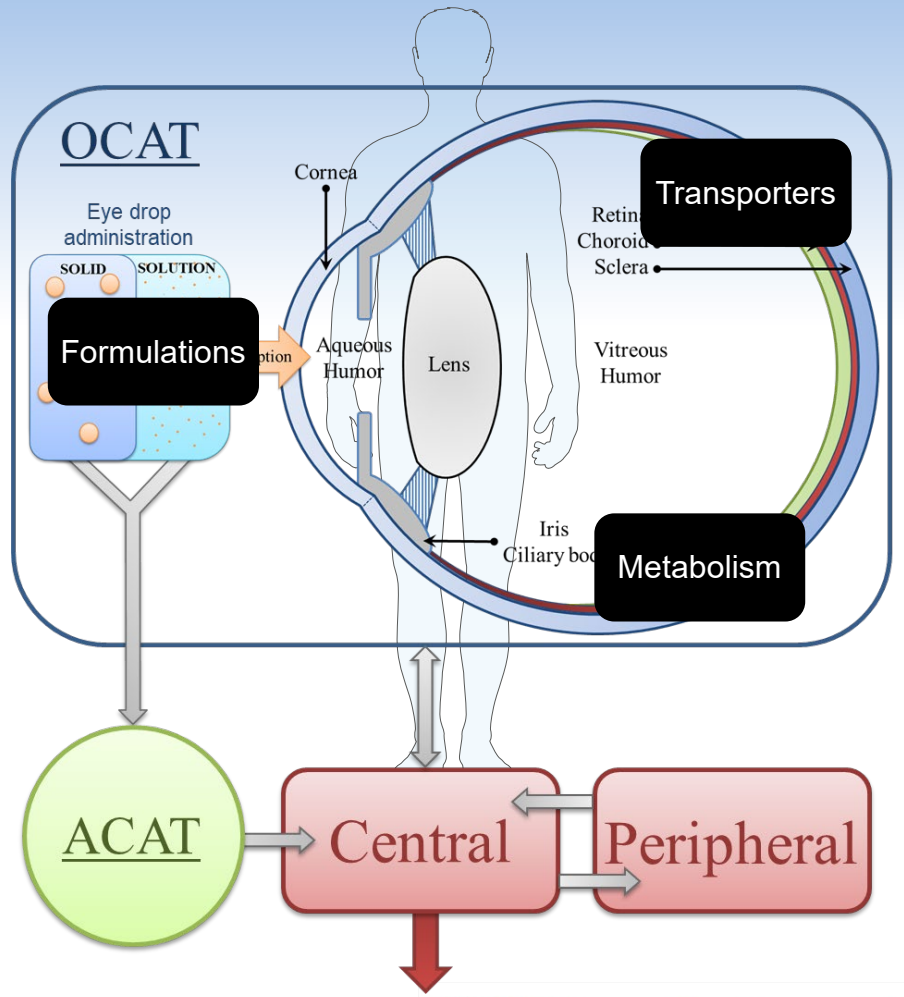
1. Yellepeddi VK, Palakurthi S. Recent Advances in Topical Ocular Drug Delivery. J Ocul Pharmacol Ther. 2016;32(2):67-82.
2. LeMerdy M, Fan J, et al. Application of Mechanistic Ocular Absorption Modeling and Simulation to Understand the Impact of Formulation Properties on Ophthalmic Bioavailability in Rabbits: A Case Study using Dexamethasone Suspension. *In submission.*
3. Schoenwald RD, Stewart P. Effect of particle size on ophthalmic bioavailability of dexamethasone suspensions in rabbits. J Pharm Sci. 1980;69(4):391-4.

Dr. Le Merdy was supported in part by an appointment to the ORISE Research Participation Program at CDER through an interagency agreement between the US Department of Energy and the US FDA (identified with *).

Next steps:

Extrapolation





Since 2018:

- Contract with Simulation Plus
- 5 year plan, including *in vitro*, pre-clinical, and clinical studies to support model development & verification

SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

Conclusions and discussion

- Numbers of applications (NDA, ANDA) supported by PBPK modeling has increased significantly since 2008
- The FDA is investing time & money to improve the science supporting PBPK model development
- Multiple on-going projects and new conclusions should reach the public in the near future
- **As we are learning, the FDA is learning too**

Conclusions and discussion

PRE-CONFERENCE PROGRAMS

PBPK MODELING FOR THE DEVELOPMENT AND APPROVAL OF LOCALLY ACTING DRUG PRODUCTS

WEDNESDAY, MARCH 13, 2019 | 8:00 AM – 5:00 PM

9:20 AM – 9:40 AM
Impact of Orally Inhaled and Nasal Drug Product PBPK Models on Product Development and Regulatory Decision Making
SPEAKER
Ross Walenga, PhD
US Food and Drug Administration, Silver Spring, MD

8:20 AM – 8:40 AM
Using PBPK to Link Systemic PK to Local Delivery in the Lung
SPEAKER
Guenther Hochhaus, PhD
University of Florida, Gainesville, FL

3:30 PM – 3:50 PM
Challenges in Using PBPK Models for Locally Acting Drug Products to Inform Regulatory Decision Makings
SPEAKER
Liang Zhao, PhD
US Food and Drug Administration, Silver Spring, MD

11:20 AM – 11:40 AM
PBPK Modeling for the Development of Dermatological Drug Products and its Regulatory Impact
SPEAKER
Eleftheria Tsakalozou, PhD
US Food and Drug Administration, Silver Spring, MD

1:50 PM – 2:10 PM
Developing PBPK for Ocular Delivery
SPEAKER
Michael B. Bolger, PhD
Simulations Plus, Lancaster, CA

2:10 PM – 2:30 PM
Use of PBPK Model to Evaluate Impact of Ophthalmic Drug Product's Critical Quality Attributes on BA/BE Assessment
SPEAKER
Andrew Babiskin, PhD
US Food and Drug Administration, Silver Spring, MD

Questions?