Mechanistic Modeling and Simulation Approaches for Performance Prediction of Locally Acting Complex Drug Products

2022 PharmSci 360

Hot Topic Session:

Preclinical development of complex locally acting drug products: Novel approaches to accelerate the access to patients

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Learning Objectives

1. Introduce the concept of Mechanistic Modeling and Simulation Tools and highlight their potential applications and advantages over traditional approaches for drug product development and bioequivalence assessment.
2. Describe the “building blocks” of the discussed in-silico tools and the data requirements for developing them with a primary focus on formulation and/or device attributes.
3. Provide examples of topical dermatological, nasally inhaled and ophthalmic drug products where mechanistic modeling and simulation approaches were used to elucidate the relationship between drug product attributes and drug product in vivo performance.
4. Highlight the best practices when utilizing the discussed silico tools, the challenges associated with model performance assessment (validation/credibility) and the constantly expanding capabilities of mechanistic modeling and simulation approaches.

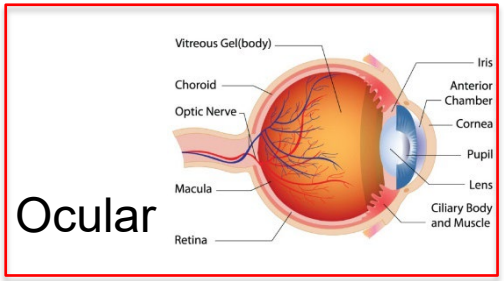
Outline

- Mechanistic Modeling and Simulation Tools For Locally-Acting Generic Drug Products
  - Applications
  - Advantages
  - “Building blocks”
- Case Studies
  - Dermatological drug products
  - Nasally inhaled drug products
  - Ophthalmic drug products
- Future Directions

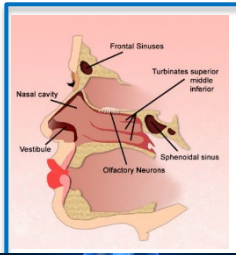
Mechanistic Modeling and Simulation Tools for Locally-Acting Drug Products

Drug Substance Formulation CQAs → **Physiological System** → **In vivo Performance**

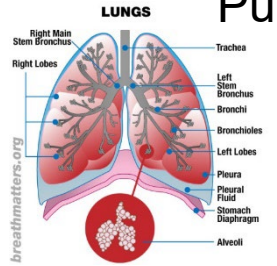
Predict **systemic** AND **local** concentrations



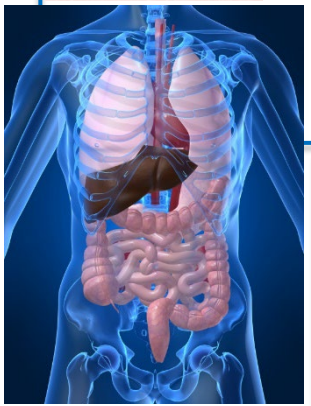
Ocular

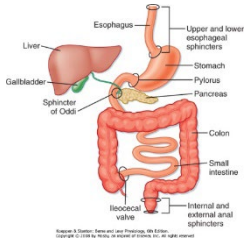


Nasal

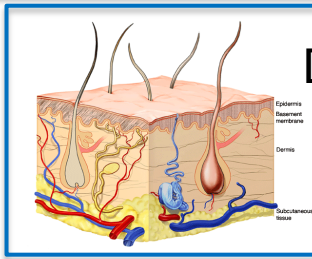


Pulmonary





GI



Dermal

Adapted from Dr. Liang Zhao

Based on the publication by Jiang W, Kim S, Zhang X, Lionberger RA, Davit BM, Conner DP, Yu LX. Int J Pharm. 2011 Oct 14;418(2):151-60.

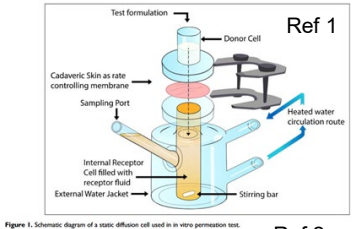
Mechanistic Modeling and Simulation Tools For Locally-Acting Drug Products

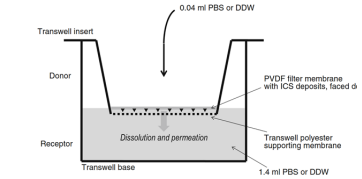
- ***Physiologically-based pharmacokinetic (PBPK) modeling***
  - Predictions of local and systemic active pharmaceutical ingredient (API) exposure
  - Integration of information on physiology, drug and drug product
  - Validated with in vitro or in vivo data
- ***Computational Fluid Dynamics (CFD) Modeling***
  - Prediction of fluid and particle transport
  - Allows for consideration of realistic geometries
  - Validated with in vitro or in vivo data

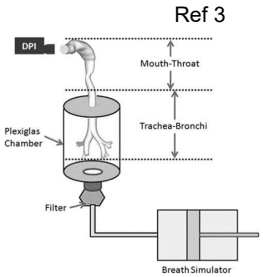
Mechanistic Modeling and Simulation Tools For Locally-Acting Drug Products

- Purpose
  - Address challenges with comparative in vitro characterization data, comparative clinical endpoint and pharmacokinetic (PK) endpoint bioequivalence (BE) studies
  - Support alternative BE approaches that do not include comparative clinical endpoint studies
  - Supplement alternative BE approaches that are centered around a detailed in vitro characterization approach for BE
  - Support Product-Specific Guidance development
  - Support aspects of performing biorelevant in vitro testing studies
  - Elucidate the relationship between drug product/device characteristics, local API amounts, and systemic exposure
- Advantages
  - Integrate information on physiology (population and subpopulations), API (physicochemical properties), drug product attributes and device parameters to provide informed predictions on in vivo performance
  - Prediction of exposure at or close to the site of action where sampling is not feasible, not ethical or challenging for reasons such as increased study cost and limited sample size not allowing conclusions to be drawn
  - Decrease the need for human studies that may be costly, not feasible or not the most sensitive or discriminatory method for detecting formulation differences

Mechanistic Modeling and Simulation Tools for generic drug products: “building blocks”

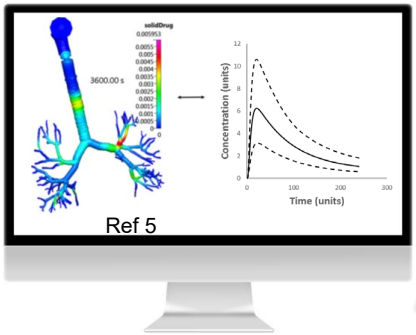


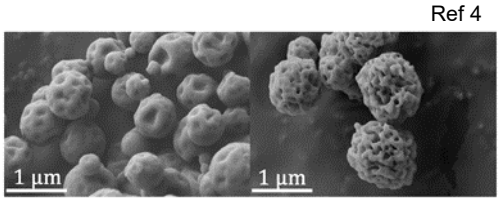




In vitro Product Performance

Human Physiology in Individuals/Populations





Drug Product Characterization

Case Study 1: Dermal PBPK model for Metronidazole Topical Products

Mechanistic Modeling of In Vitro Skin Permeation and Extrapolation to In Vivo for Topically Applied Metronidazole Drug Products Using a Physiologically Based Pharmacokinetic Model

Sumit Arora,* James Clarke, Eleftheria Tsakalozou, Priyanka Ghosh, Khondoker Alam, Jeffery E. Grice, Michael S. Roberts, Masoud Jamei, and Sebastian Polak

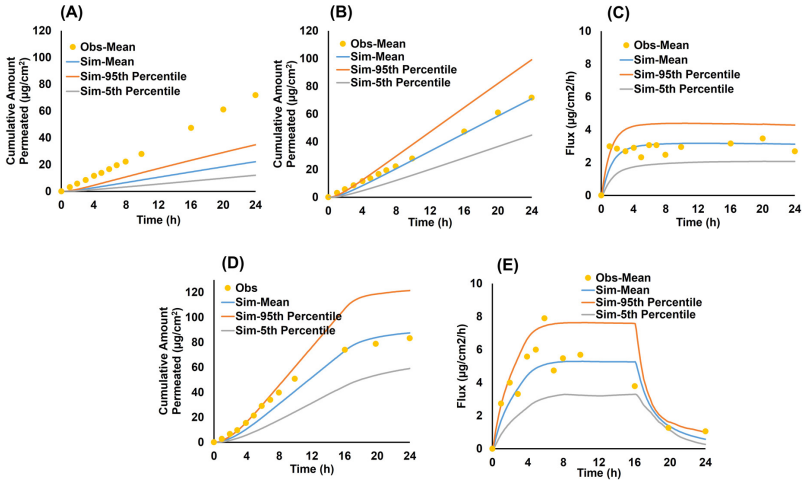
- Grant # U01FD006522: University of Queensland/Certara UK, 2018-2021
- Metronidazole topical dermatological drug products are applied on the skin surface to treat skin diseases
- Objective: *Use the dermal PBPK model (MPML MechDermA, Simcyp Simulator, Certara), validated with in vitro permeation testing (IVPT) study data, to predict in vivo metronidazole amounts in the skin*[6]

Case Study 1: Dermal PBPK model for Metronidazole Topical Products

$Kp_{sclip/water}$

Simple aqueous metronidazole solutions

1. Metronidazole solubility
2. Water viscosity



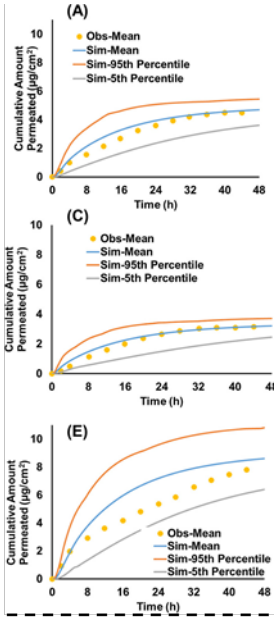
Case Study 1: Dermal PBPK model for Metronidazole Topical Products

$Kp_{sclip/water}$

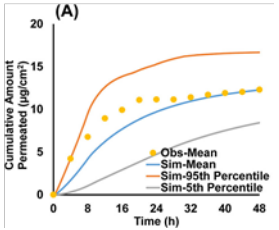
Simple aqueous metronidazole solutions
1. Metronidazole solubility
2. Water viscosity

MetroGel® (metronidazole) topical gel, 0.75%
1. Formulation pH
2. Apparent viscosity
3. Metronidazole solubility in continuous phase of gel
4. Drying profile
5. Precipitation (assumed, empirical)

Murthy et al.



Roberts et al.



Case Study 1: Dermal PBPK model for Metronidazole Topical Products

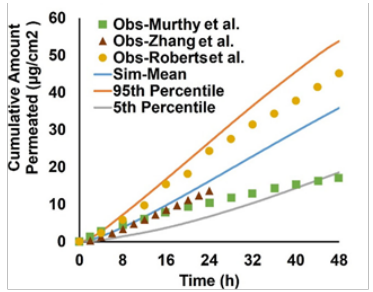
$Kp_{sclip/water}$

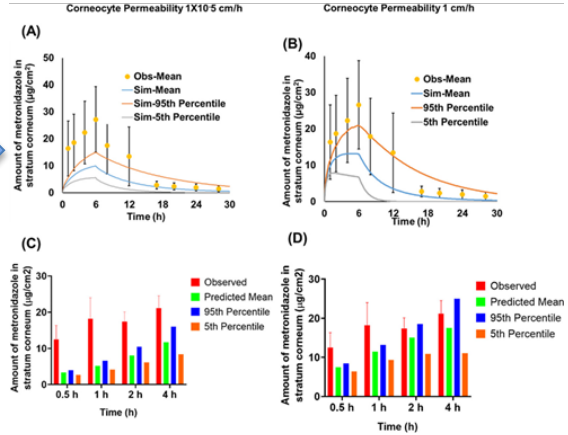
Simple aqueous metronidazole solutions
1. Metronidazole solubility
2. Water viscosity

MetroGel® (metronidazole) topical gel, 0.75%
1. Formulation pH
2. Apparent viscosity
3. Metronidazole solubility in continuous phase of gel
4. Drying profile
5. Precipitation (assumed, empirical)

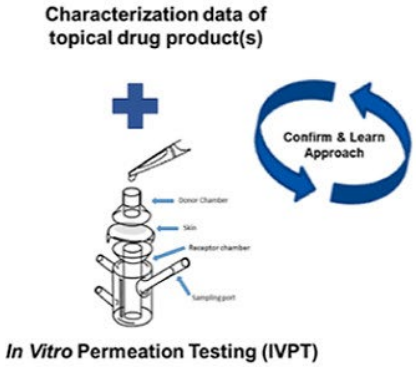
D_{sclip} and P_{corn}

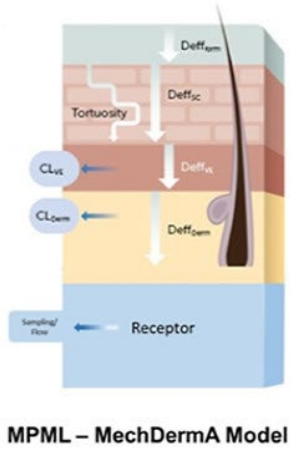
MetroCream® (metronidazole) topical cream, 0.75%
1. Formulation pH
2. Apparent viscosity
3. Metronidazole solubility in continuous phase of cream
4. Formulation composition
5. Globule size distribution
6. Drying profile
7. Precipitation (assumed, empirical)

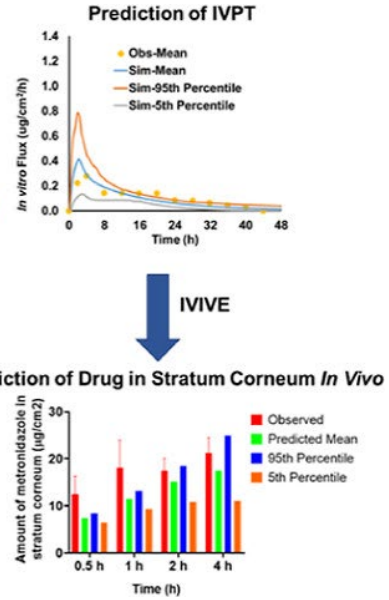




Case Study 1: Dermal PBPK model for Metronidazole Topical Products



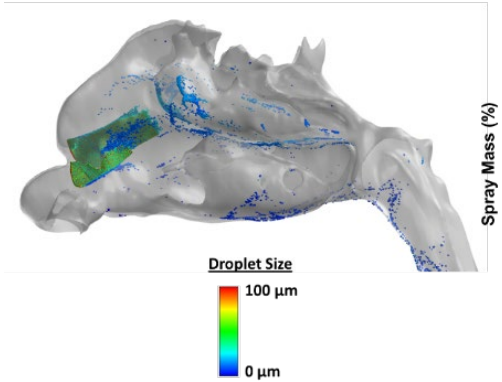




The developed model via the established in vitro in vivo extrapolation (IVIVE) described reasonably well

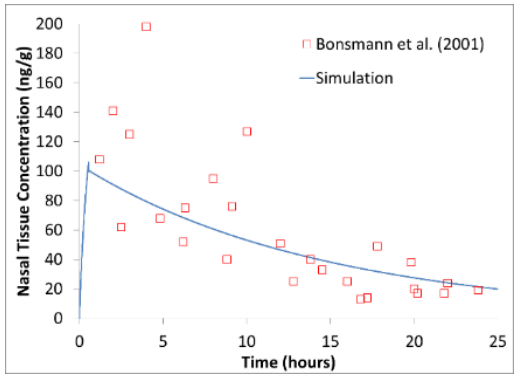
- ✓ formulation metamorphosis
- ✓ in vitro skin permeation by accounting for several drug product quality attributes
- ✓ metronidazole amount in the stratum corneum in vivo

Case Study 2: Hybrid CFD-PBPK for Nasally Inhaled Corticosteroids



CFD predictions for deposition locations of fluticasone propionate droplets, from Kimbell et al.[7]

PK predictions of fluticasone propionate nasal spray, from Schroeter et al.[8]

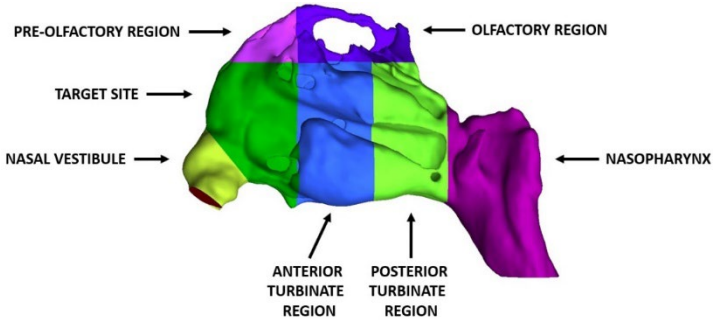


- Applied Research Associates, Inc.
  - Grant #1U01FD005201: 2014-2018
  - Contract #75F40119C10079: 2019-present
  - Principal Investigator (PI): Jeffry Schroeter
- Fully 3D CFD model predicts deposition
- PBPK model for nasal absorption
- CFD results serve as inputs to the PBPK model
  - Models are run independently
  - Constant mucociliary clearance (MCC) velocity
- Investigation of device and usage parameters

Slide courtesy of Dr. Ross Walenga

Case Study 2: Hybrid CFD-PBPK for Nasally Inhaled Corticosteroids

- In Vitro Metrics – Input Parameters
- CFD modeling was used to examine impact of various in vitro parameters on regional deposition predictions
- Input parameters were varied by ± 10% and ± 20% to understand parameter sensitivity



Regional definitions for healthy subject model MCW002
(Figure produced by ARA for contract 75F40119C10079)

CFD input parameters for several brand name drug products
(Based on table produced by ARA for contract 75F40119C10079)

Spray	Spray Cone Angle (degrees)	Dv50 (µm)	Span
Fluticasone Propionate	63.3 ± 4.2 [a]	46.4 ± 2.1 [b]	2.04 ± 0.32 [b]
Triamcinolone Acetonide	55.9 ± 0.9 [a]	43.8 ± 2.8 [a]	1.99 ± 0.27 [a]
Mometasone Furoate	20.0 ± 0.5 [c]	41.4 ± 1.1 [b]	1.91 ± 0.25 [b]
Budesonide	59.4 ± 18.3 *	29.4 ± 1.7 [b]	2.42 ± 1.23 [b]
Fluticasone Furoate	35 ± 2.1 [d]	57.1 ± 1.3 [d]	1.39 ± 0.01 [d]

[a] Next Breath report, Kimbell R01[9]

[b] Schroeter et al.[10]

[c] Xi et al.[11]

[d] Hosseini et al.[12]

* Estimated valued based on Shrestha et al.[13]

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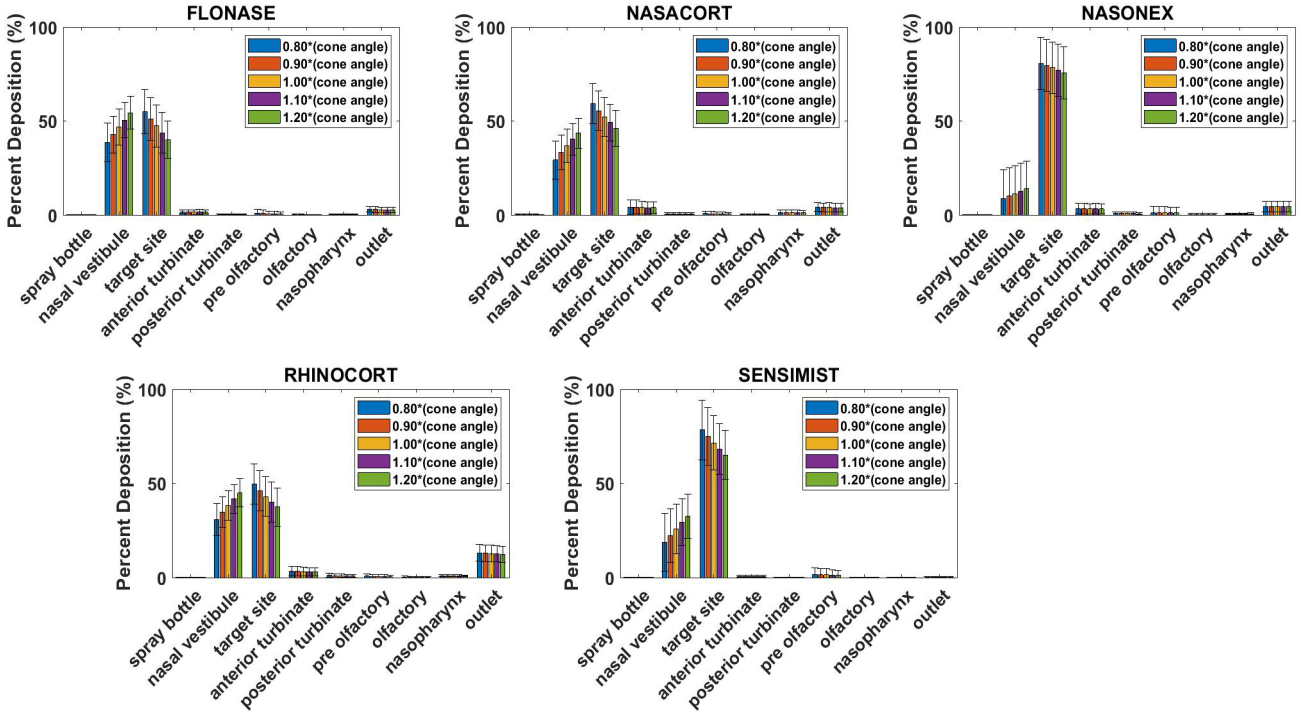
Case Study 2: Hybrid CFD-PBPK for Nasally Inhaled Corticosteroids

Sensitivity of Regional Deposition to In Vitro Metric Variation



Regional deposition results for fluticasone propionate nasal spray (Flonase®), triamcinolone acetonide nasal spray (Nasacort®), mometasone furoate nasal spray (Nasonex®), budesonide nasal spray (Rhinocort), and fluticasone furoate nasal spray (Flonase Sensimist) (Based on figures produced by ARA for contract 75F40119C10079)

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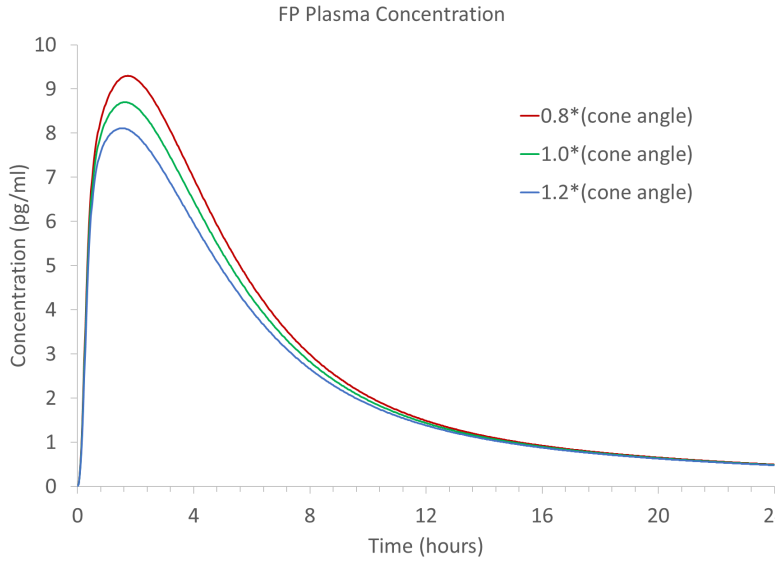
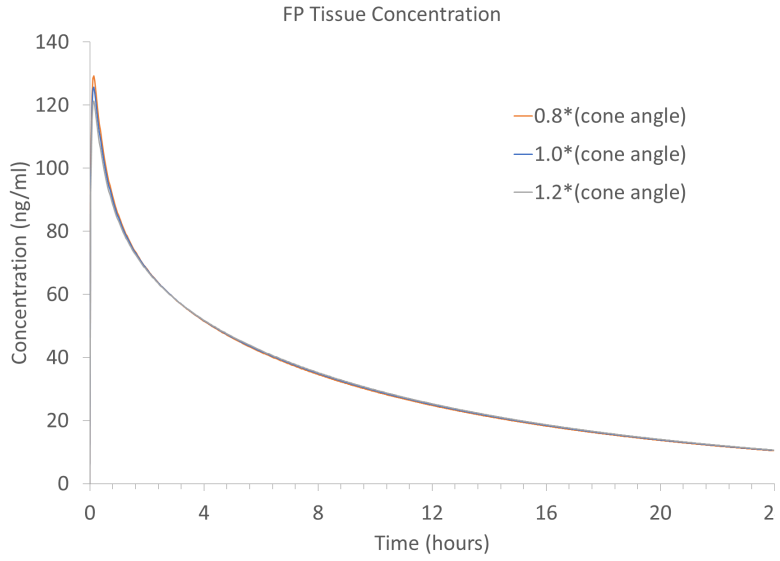
Case Study 2: Hybrid CFD-PBPK for Nasally Inhaled Corticosteroids

Impact of Spray Cone Angle on PK



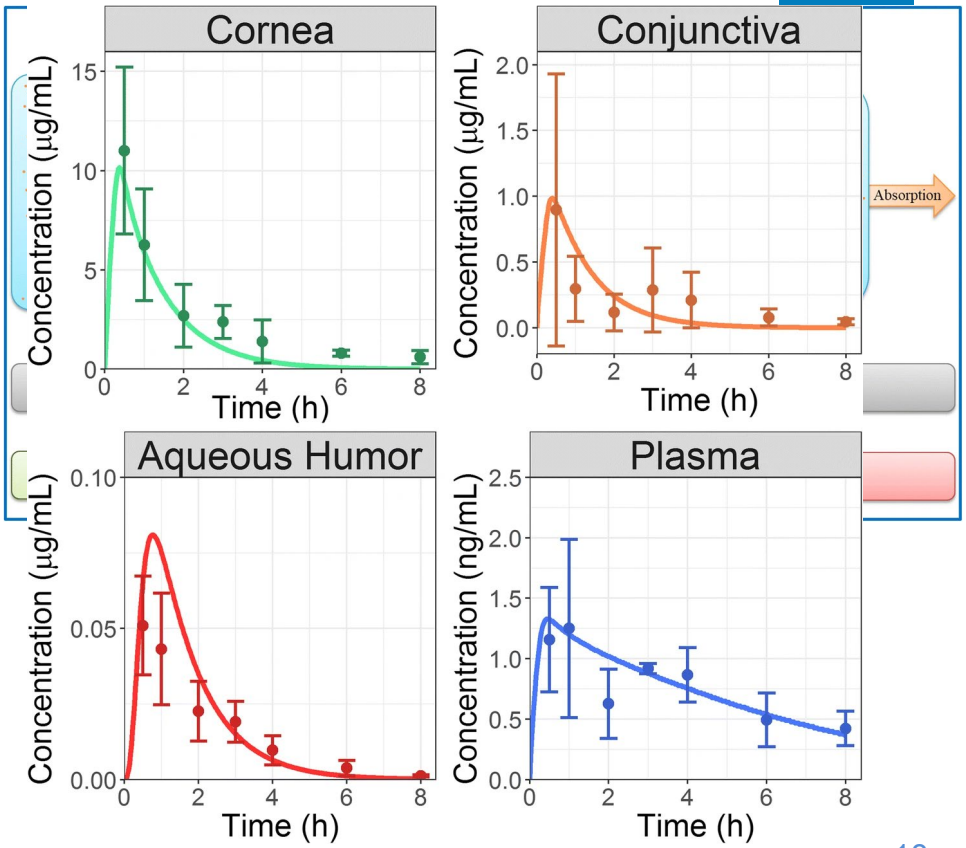


Systemic and tissue PK predictions for fluticasone propionate (FP) nasal spray based on differences in spray cone angle (Based on figures produced by ARA for contract 75F40119C10079)

Slide courtesy of Dr. Ross Walenga

Case Study 3: Ocular PBPK model for Dexamethasone Ophthalmic Suspensions

- Dexamethasone (Dex) suspensions prescribed for inflammatory ocular conditions
- Objective: *Use validated rabbit OCAT™ PBPK model (GastroPlus™, Simulations Plus) to study formulation effect on API ocular exposure*
- Ocular PBPK model development and assumptions[14,15]
  - Dissolution rate per Lu et al., 1993[16] accounting for Dex mean particle size
  - Tear volume, changing dynamically with time, was modeled based on physiology considerations and accounting for formulation attributes (viscosity)
  - Viscosity modeled indirectly under the assumption that it impacts the nasolacrimal drainage
- Model validation
  - TOBRADEX ST® 0.05% in rabbit eye[15]

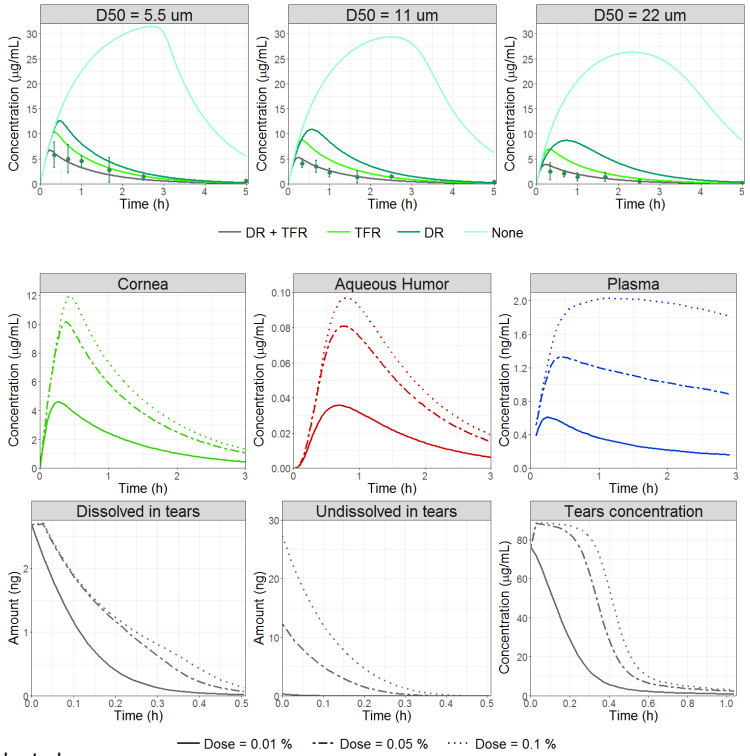


Slide courtesy of Dr. Mingliang Tan, adapted

Case Study 3: Ocular PBPK model for Dexamethasone Ophthalmic Suspensions

- Tear production and nasolacrimal drainage contribute to API elimination following the administration of three suspensions of Dex 0.1% with differing particle size

- Non-linear PK is predicted following application of Dex 0.01%, 0.05% and 0.1%
  - Drug dissolved and undissolved predicted amounts in the tear



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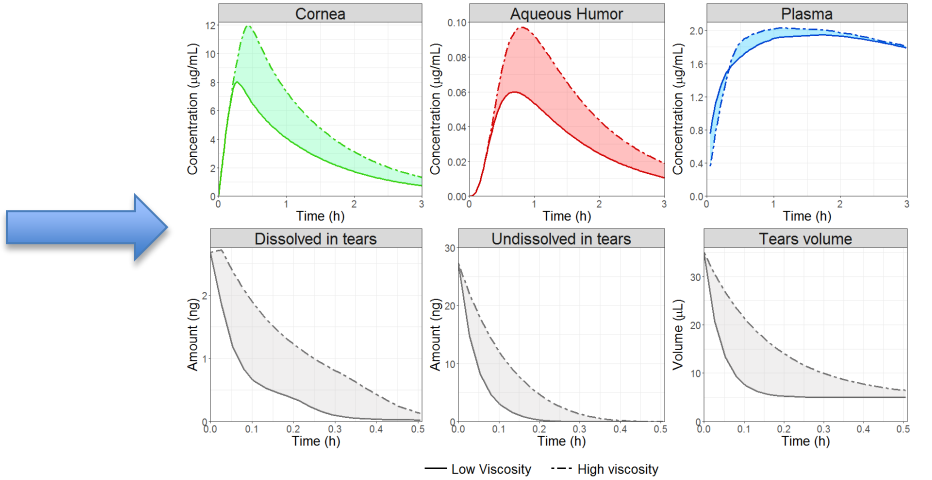
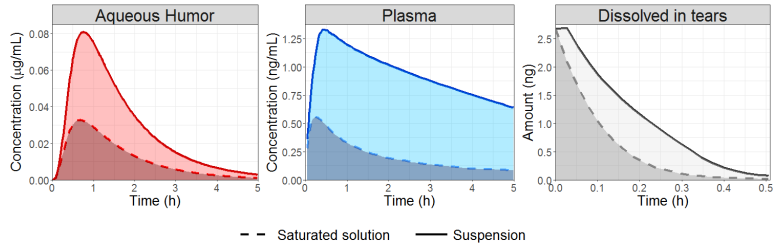
Case Study 3: Ocular PBPK model for Dexamethasone Ophthalmic Suspensions

- Dex 0.1% ophthalmic suspensions with different viscosities (low and high)
  - Increase in viscosity increases cornea and aqueous humor exposure to a larger extent than plasma exposure per model predictions
  - Higher viscosity is predicted to result in higher Dex exposure in tears and in higher tear volume



- Undissolved API (suspension) contributes to overall ocular and plasma exposure



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Future Directions

- Model validation/model credibility with in vivo and/or in vitro data
  - Impact of CQAs and device characteristics on predictions
  - Utilize appropriate datasets
- Accurately capture physiology or human geometry
- Account for dynamic changes the product undergoes post application, impact on API delivery, release and uptake/absorption
- Account for the interplay between the drug product and the application site (physiology)
- Expand model capabilities:
  - Interspecies extrapolations
  - Healthy and diseased populations
  - Assessment of biopredictiveness of in vitro characterization methodologies
- Considerations when simulating virtual BE (VBE) trials
  - Accounting for inter- and intra-subject variability

Take Home Messages

- Mechanistic Modeling and Simulation is used to support generic approval and ANDA submissions

- Complex generic locally-acting drug products may benefit from model integrated approaches supporting product development approval, which may be facilitated via pre-ANDA meetings with the U.S. FDA

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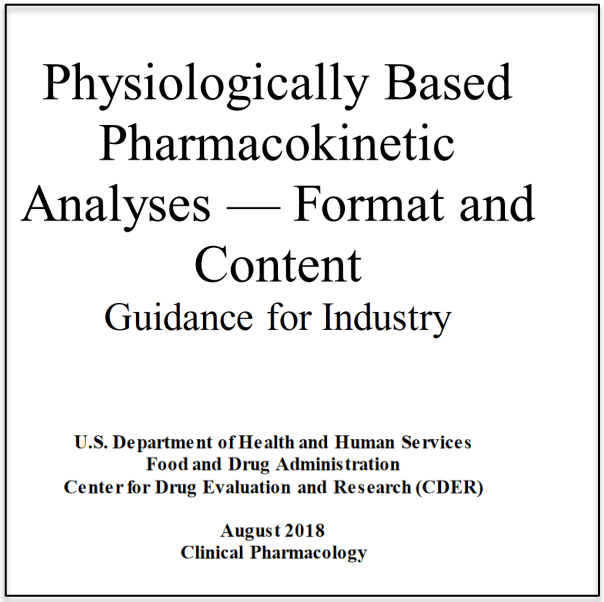
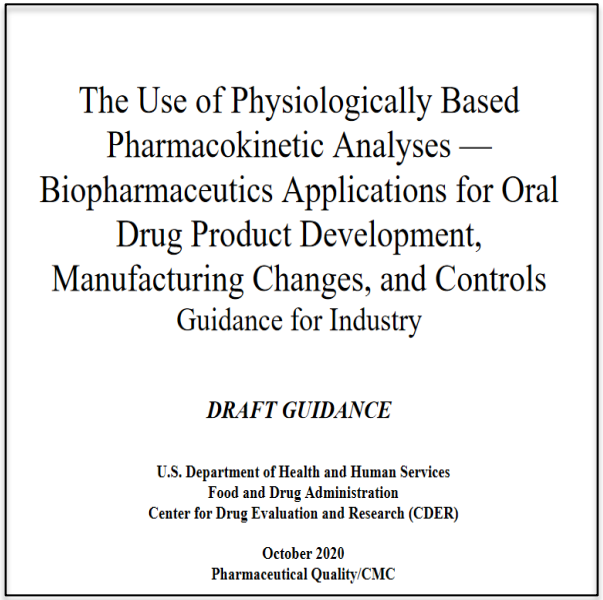
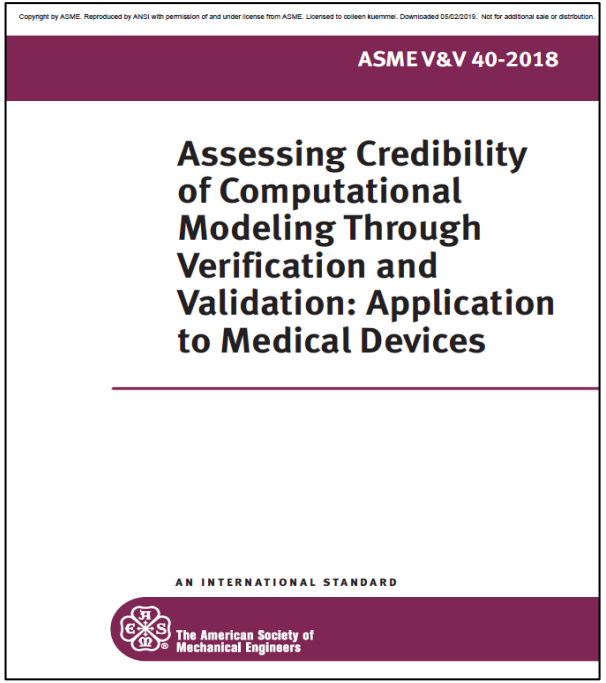
Applicants are encouraged to follow best practices when developing mechanistic models for regulatory submissions[17,18]







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Questions?

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Division of Quantitative Methods and Modeling
Office of Research and Standards, Office of Generic Drugs
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