Mechanistic Drug Delivery Models

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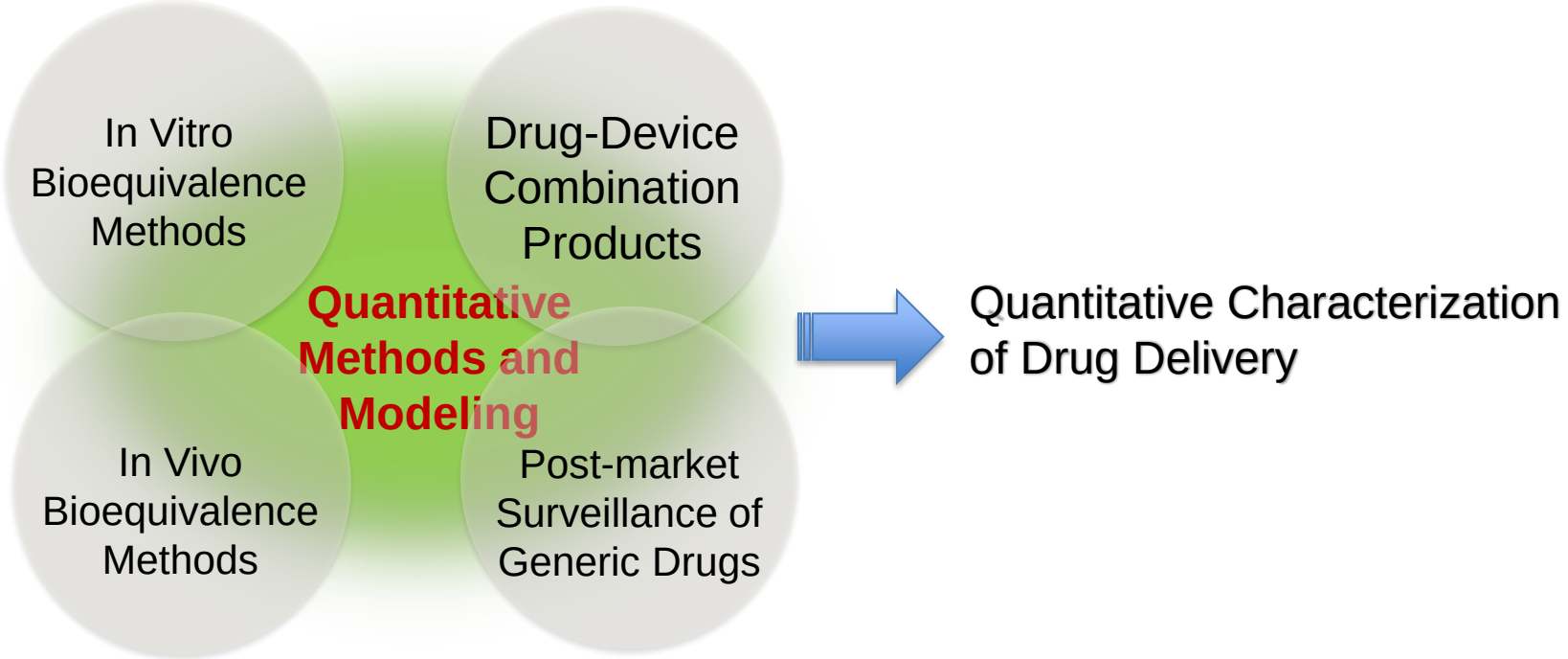
Disclaimer

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

The presenter is offering his perspective based upon his experiences during regulatory decision-making

Quantitative Methods & Modeling (QMM) for Generic Drug Development and Approval



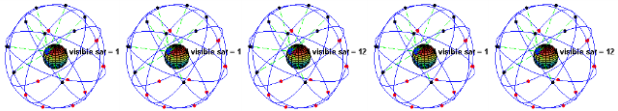
Model-integrated evidence (MIE) refers to using model generated information such as the virtual bioequivalence (VBE) study results not just to plan a pivotal study but to serve as pivotal evidence

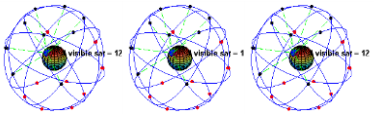
Clin Pharmacol Ther. 2019 Feb;105(2):338-349

What Are the Drug Development Failure Modes?

Research/Discovery

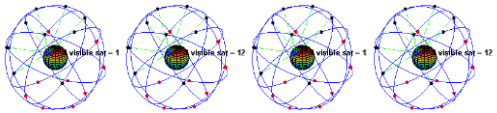
- Ineffective disease target
  - Lack of efficacy
  - On target safety
- Ineffective design of drug molecule
  - Chemical, biologics, RNAs, and Gene therapies
  - Mechanism of action; off target effect



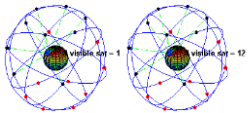


Development

- Failed drug delivery
  - State of art formulation
  - Common challenge for oligonucleotide treatment



- Wrong dose/dosing regimen/trial design

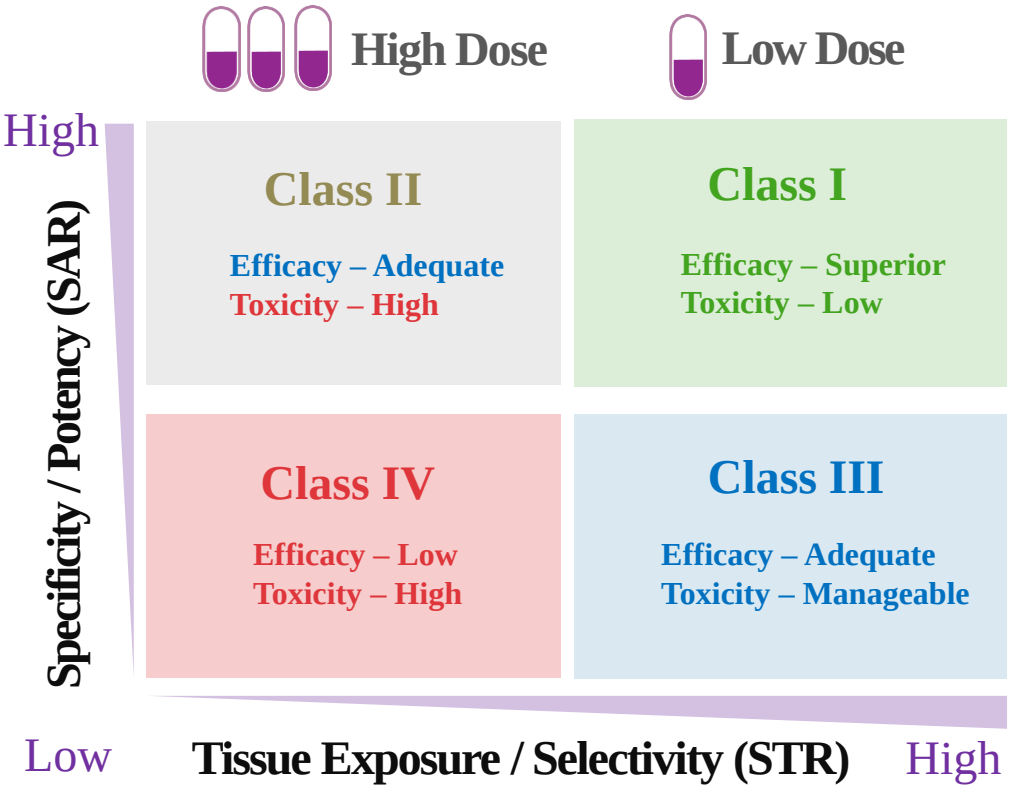


Importance

Why 90% of Clinical Drug Development Fails and How to Improve It?
STAR (Structure-Tissue Exposure/Selectivity-Activity-Relationship) Selects Better Drug Candidates and Balances Clinical Dose/Efficacy/Toxicity

II
Low Success Rate
Evaluate Cautiously
Possible Successful Examples:
Ibrutinib (I)? Remdesivir (IV)?
Spebrutinib (failed)
Many Failed In Clinical Trials

IV
Lowest Success Rate
Terminate Early
Possible Successful Examples:
Almost None
Most Failed In Clinical Trials

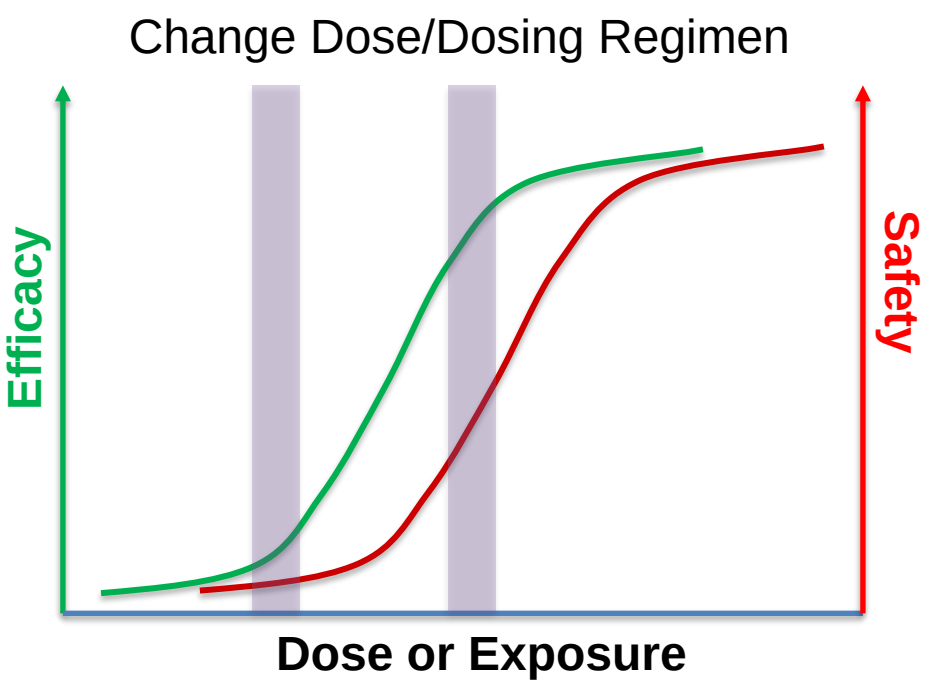


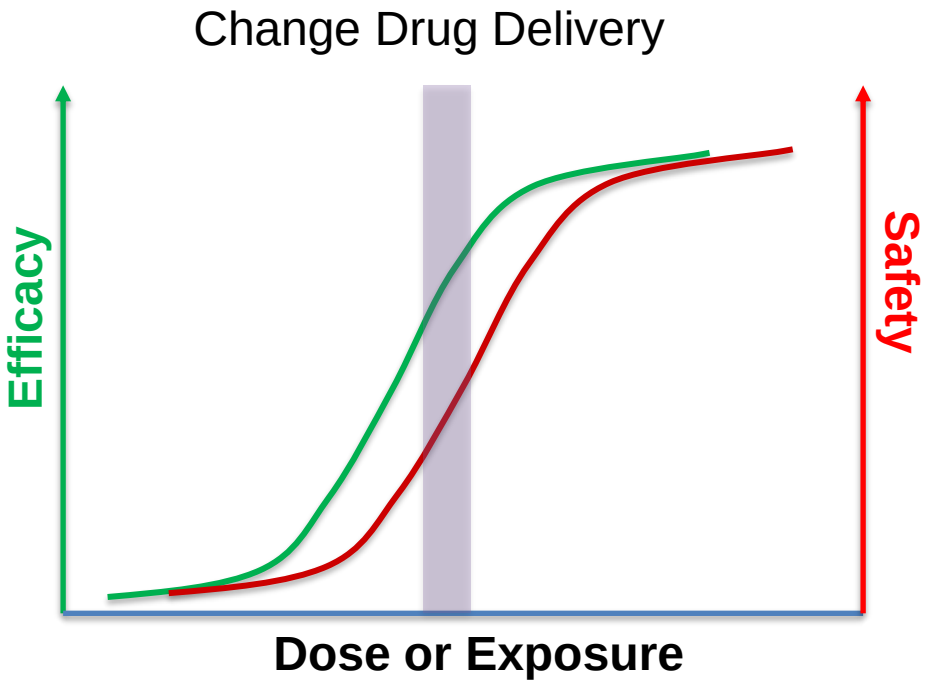
I
Best Success Rate
Most Desirable
Possible Successful Examples:
Viagra, Sofosbuvir, Lipitor, Acalabrutinib, Tamoxifen, Pomalidomide, Propranolol, Famotidine, Clarinex, More

III
Good Success Rate
Often Overlooked
Possible Successful Examples:
Thalidomide? Claritin?
Many Mistakenly Terminated

Sun D, et al. Acta Pharm Sin B. 2022. Slide Adapted from Dr. Duxin Sun

Change Dosing vs Changing Delivery





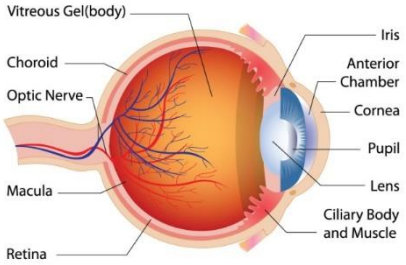
How to change drug delivery: API design, route of administration, and formulation

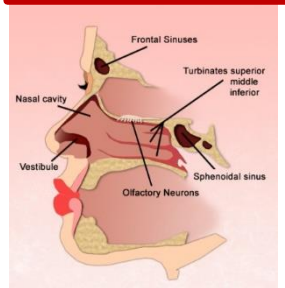
Drug Delivery Models

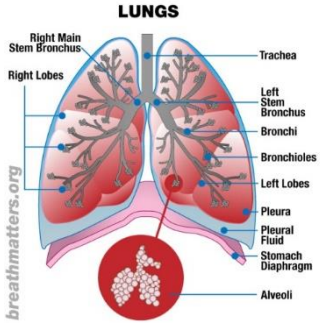
- Oral Absorption
- Orally inhaled
- Intranasal drug delivery
- Ophthalmic
- Topical dermatological
- Female reproductive tract/rectal/otic
- Oligonucleotide delivery (e.g., mRNA)

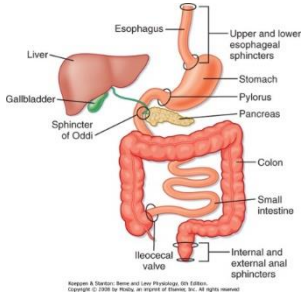
Physiologically Based Models for Drug Delivery

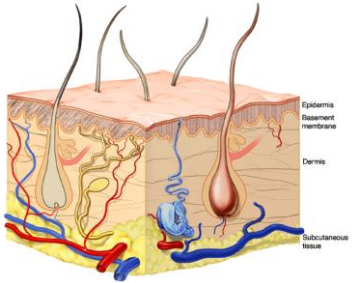
Drug Substance Formulations In Vitro Testing → **Physiological System** → **In Vivo Performance**











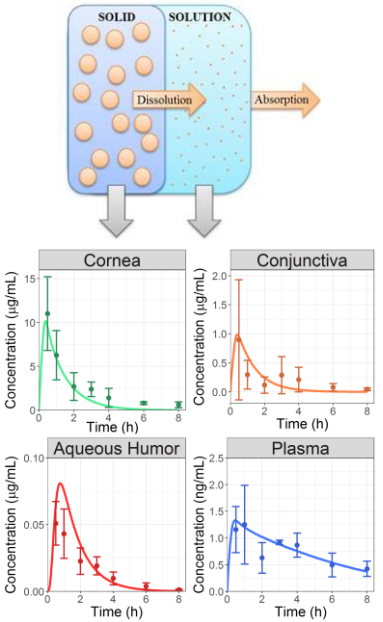
Based on the publication by Jiang W, Kim S, Zhang X, Lionberger RA, Davit BM, Conner DP, Yu LX. Int J Pharm. 2011 Oct 14;418(2):151-60.

Case 1

Recognize Critical Quality Attribute (CQA) for Ophthalmic Suspensions

Case study - Dexamethasone

- After instillation, several routes of dexamethasone transport:
  - Dissolved dexamethasone diffusing from tear film through cornea or conjunctiva
  - Solid particles and dissolved dexamethasone cleared from eye surface through nasolacrimal drainage -> systemic circulation
- OCAT Model Development – internally conducted rabbit study with PK sampling from multiple ocular tissues and plasma
- Model Verification with multiple datasets showing:
  - Particle size impact on ocular absorption
  - Viscosity impact on ocular absorption
  - Non-linear dose-exposure relationship

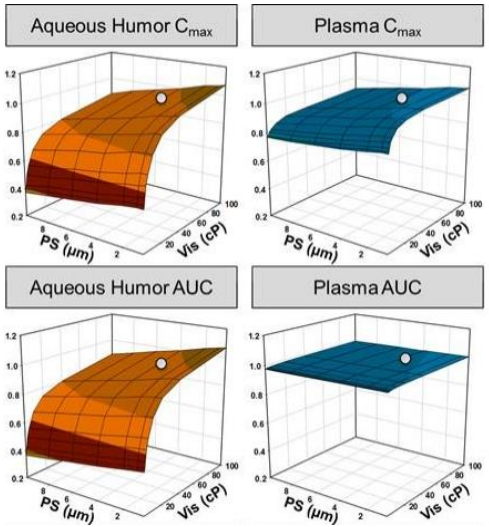


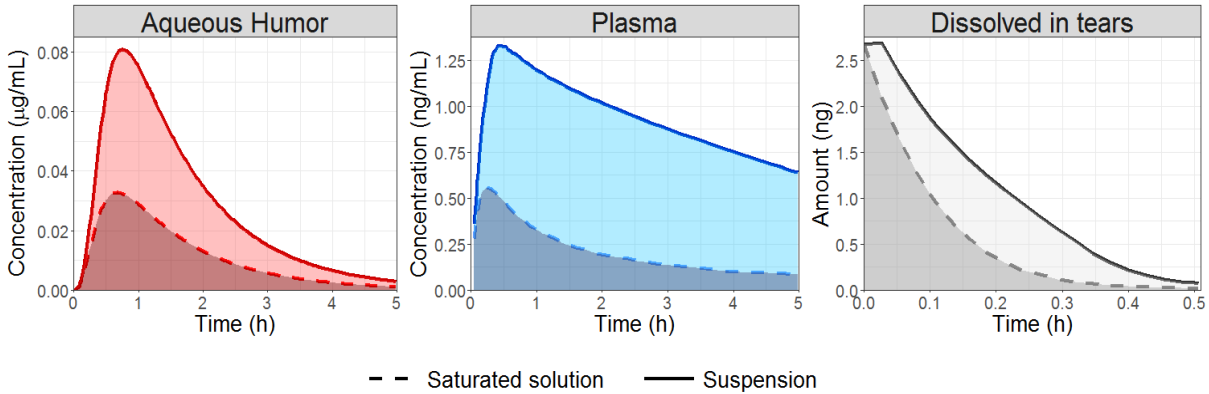
Chockalingam, Ashok, et al. "Protocol for evaluation of topical ophthalmic drug products in different compartments of fresh eye tissues in a rabbit model." Journal of pharmacological and toxicological methods 96 (2019): 9-14.
LeMerdy, Maxime, et al. "Application of Mechanistic Ocular Absorption Modeling and Simulation to Understand the Impact of Formulation Properties on Ophthalmic Bioavailability in Rabbits: A Case Study using Dexamethasone Suspension." The AAPS Journal 21.4 (2019): 65

Case 1 Summary

Recognize Critical Quality Attribute (CQA) for Ophthalmic Emulsions

Case study – Dexamethasone (cont'd)





Parameter sensitivity analysis in rabbit on PS and viscosity

- Viscosity is a critical attribute affecting BE
- Plasma/systemic PK is not reflective of local concentrations

Saturated solution vs. suspension simulations

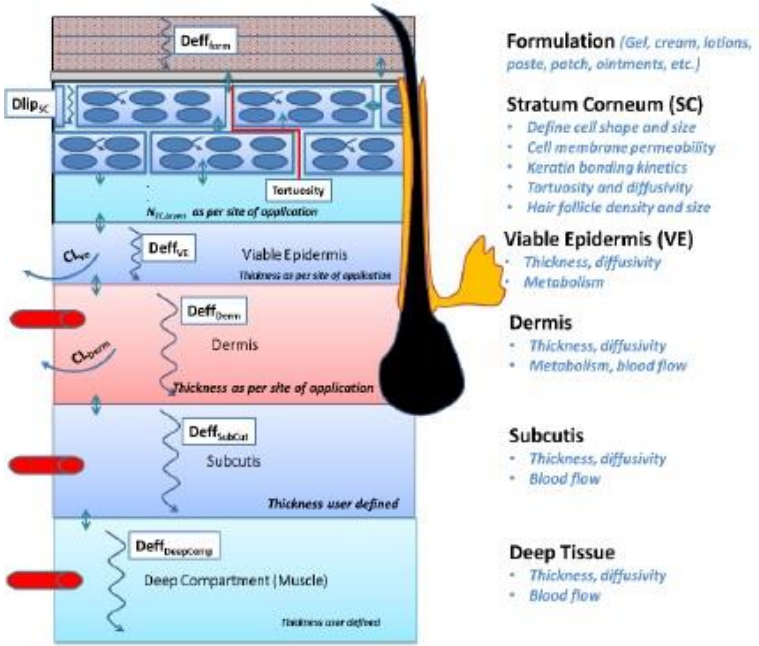
- Solid particles in formulation leads to higher aqueous humor concentrations, BUT …
- Also higher systemic exposure
- A tool for product development that can weigh benefits and risks

LeMerdy, Maxime, 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." The AAPS Journal 21.4 (2019): 65

Le Merdy, Maxime, et al. "Physiologically based pharmacokinetic model to support ophthalmic suspension product development." The AAPS journal 22.2 (2020): 1-10.

Case 2

Dermal PBPK Model to Supporting Diclofenac Sodium Topical Gel, 1% Approval



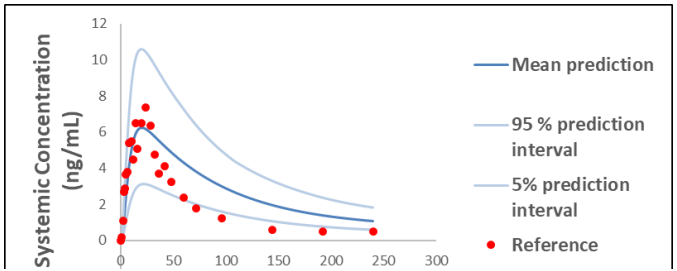
- Diclofenac sodium topical gel, 1%
- Alternative BE approach for a Q1/Q2/Q3 formulation: dermal PBPK model supported alternative to in vivo comparative clinical endpoint BE study
- Model development:
  - API physicochemical properties
  - API ADME properties
  - Formulation attributes for Reference and Test drug products (e.g., viscosity, globule size, pH)

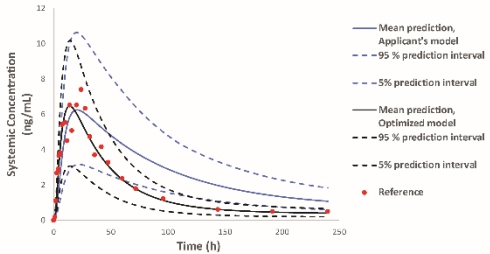
API: active pharmaceutical ingredient; ADME: absorption, distribution, metabolism, and elimination

Tsakalozou et al. CPT Pharmacometrics Syst Pharmacol. 2021 Feb 6. doi: 10.1002/psp4.12600

Case 2

Dermal PBPK Model to Supporting Diclofenac Sodium Topical Gel, 1% Approval





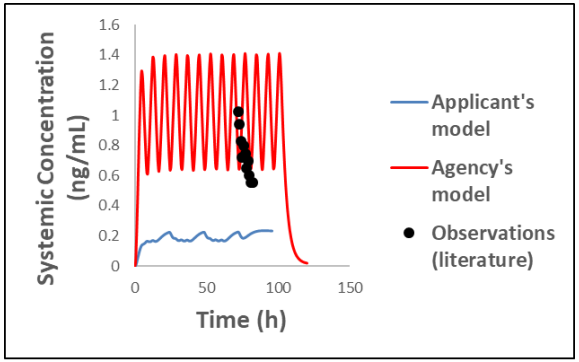
- Platform performance assessment:
  - >10 PBPK models for TDS and topical products
  - Multiple doses/product strengths and dosing regiments
  - Satisfactory model performance
- Model performance assessment for diclofenac sodium topical gel, 1%:
  - Literature and application data on doses, product strengths, dosing regiments, routes of administration and local/systemic exposure data
  - Formulation attributes for R and T
  - Good predictions of systemic exposure

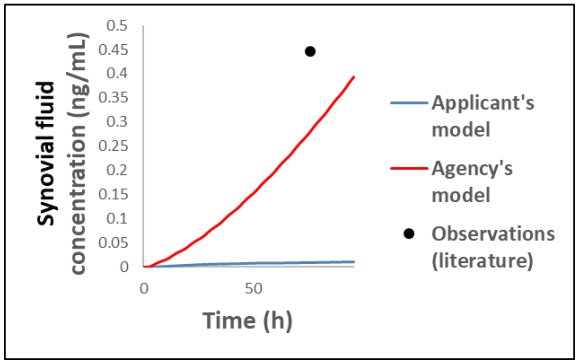
R: Reference, T: Test, TDS: Transdermal Delivery System

Tsakalozou et al. CPT Pharmacometrics Syst Pharmacol. 2021 Feb 6. doi: 10.1002/psp4.12600

Case 2

Dermal PBPK Model to Supporting Diclofenac Sodium Topical Gel, 1% Approval





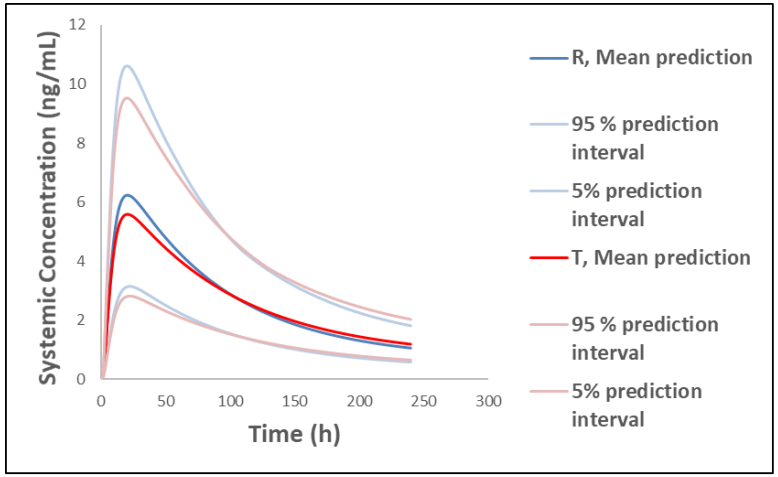
- Refined model to improve synovial fluid exposure predictions (by the Agency)
  - Protein binding in all skin layers
  - Drug product attributes updated
  - Partition coefficients modified leveraging observed local drug amounts

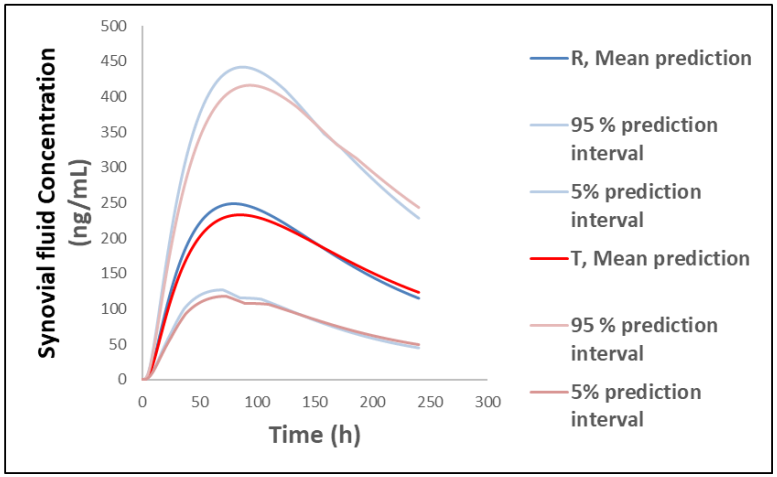
Tsakalozou et al. CPT Pharmacometrics Syst Pharmacol. 2021 Feb 6. doi: 10.1002/psp4.12600

Case 2

Dermal PBPK Model to Supporting Diclofenac Sodium Topical Gel, 1% Approval

- Conducted virtual BE assessments on predicted systemic and local exposure data
- Sensitivity analysis to check on effect of changing parameters values on conclusion
  - ✓ **R and T drug products were found bioequivalent**





R: Reference, T: Test

Tsakalozou et al. CPT Pharmacometrics Syst Pharmacol. 2021 Feb 6. doi: 10.1002/psp4.12600

Case 2 Summary

Dermal PBPK Model to Supporting Diclofenac Sodium Topical Gel, 1% Approval

- First case for using PBPK model to directly approve a product.
- PBPK models can be used to inform product development decisions and support alternative BE approaches for generic locally-acting drug products.
- Applicants are encouraged to follow best practices when developing PBPK models for generic locally-acting drug products as these are communicated by the Agency in guidances and other public forums.
- Applicants are encouraged to engage with the Agency early in their product development program by making use of the pre-ANDA meeting request program (GDUFA III).

Tsakalozou et al. CPT Pharmacometrics Syst Pharmacol. 2021 Feb 6. doi: 10.1002/psp4.12600

Case 3: Targeting Central Nervous System (CNS) Delivery with Nasal Drug Products (NDPs)

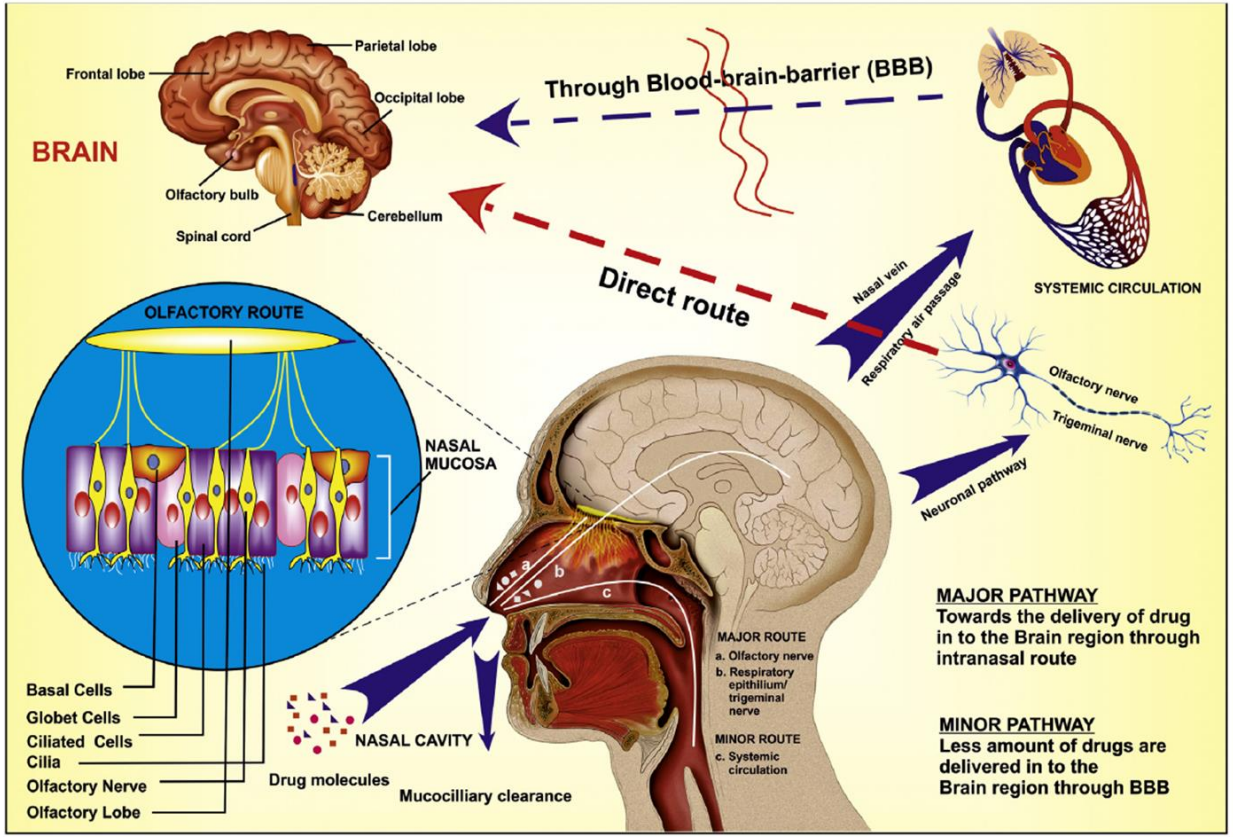
- Treat CNS disorders without the need to overcome the blood-brain-barrier
- Reduce dose needed and possibly increase rate of delivery
- Many treatments are in development
  - Alzheimer's Disease
  - Parkinson's Disease
  - Migraines

Case 3: Nasal Drug Products (NDPs) with Olfactory Targeting Claims

- Trudhesa® (dihydroergotamine mesylate nasal spray)
  - Approved September 2, 2021
  - Indicated for treatment of migraines
  - Olfactory targeting not specified on product label
- Precision Olfactory Delivery® system[1]
  - Large or small molecules, liquid or powder, to upper nasal cavity or upper turbinates
- Onzetra Xsail® (sumatriptan succinate nasal powder)
  - Approved January 27, 2016
  - Indicated for treatment of migraines
  - Olfactory targeting not specified on product label
- Optinose® system [2]
  - Aims to deliver deep into nasal cavity
  - Hypothesis that there may be local uptake via olfactory and trigeminal nerves

1. Shrewsbury et al. Headache: The Journal of Head and Face Pain. 2019;59(3):394-409.
2. Cady et al. Headache: The Journal of Head and Face Pain. 2015;55(1):88-100.

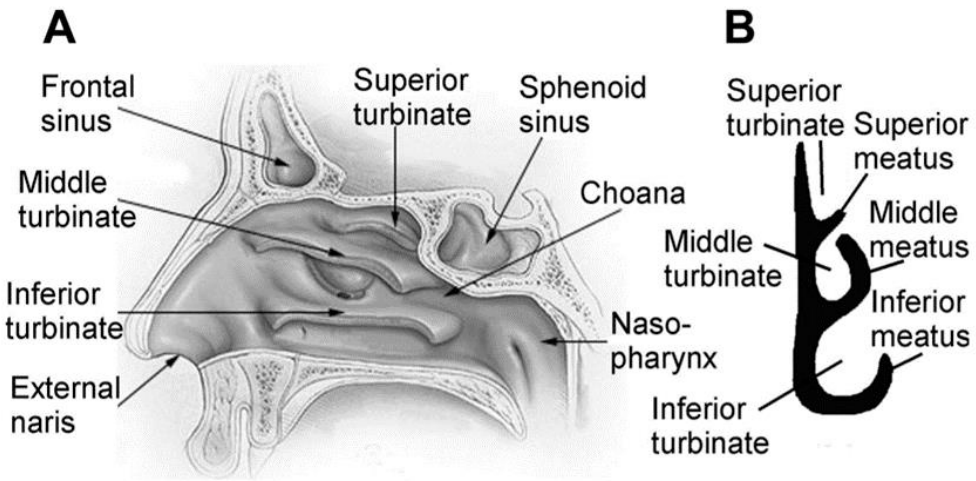
Nose-to-Brain Drug Delivery



Agrawal et al. Journal of controlled release. 2018;281:139-77.

Case 3: Bioequivalence (BE) at the Site of Action for Locally-Acting NDPs

- For locally-acting NDPs, nasal tissue is the site of action
- Regional deposition is upstream of local tissue drug exposure and systemic pharmacokinetics (PK) is downstream



Liu et al. Journal of applied physiology. 2009;106(3):784-95.

Case 3: Weight of Evidence Approach for Locally-Acting Nasal Sprays

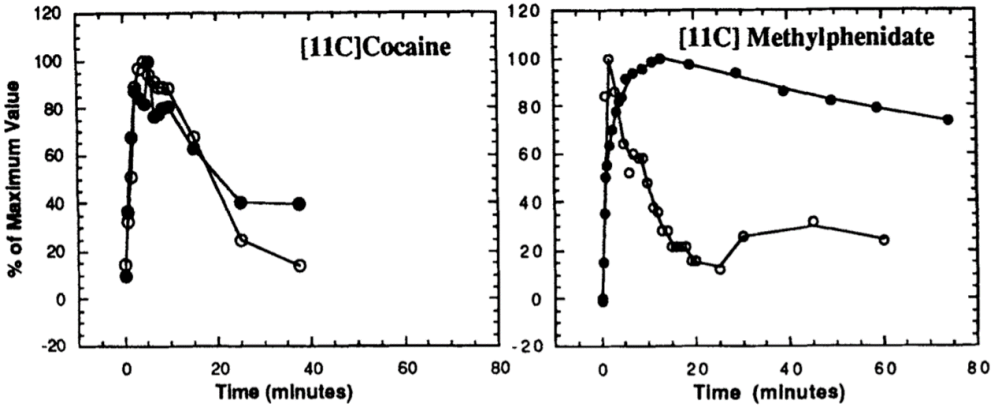
BE recommendations include in vitro studies, in vivo studies, and formulation and device sameness

In vitro studies	In vivo studies
❖ Single Actuation Content ❖ Droplet Size Distribution (DSD) by Laser Diffraction ❖ Drug in Small Particles/DSD by Cascade Impaction ❖ Spray Pattern ❖ Plume Geometry ❖ Priming and Repriming	❖ Comparative PK with fasting, two-way crossover design in healthy subjects (suspensions only) ❖ Comparative Clinical Endpoint or Pharmacodynamic (suspensions only)

U.S. Food and Drug Administration Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

Case 3: Quantification of Drug Delivery to Brain

- Receptor binding in brain may be quantified using positron emission tomography (PET) scan data
  - Ethical concerns with conducting BE study
- Alternative BE approach?
  - Combination of in vitro and/or silico studies
  - Can modeling be used to design such an approach?

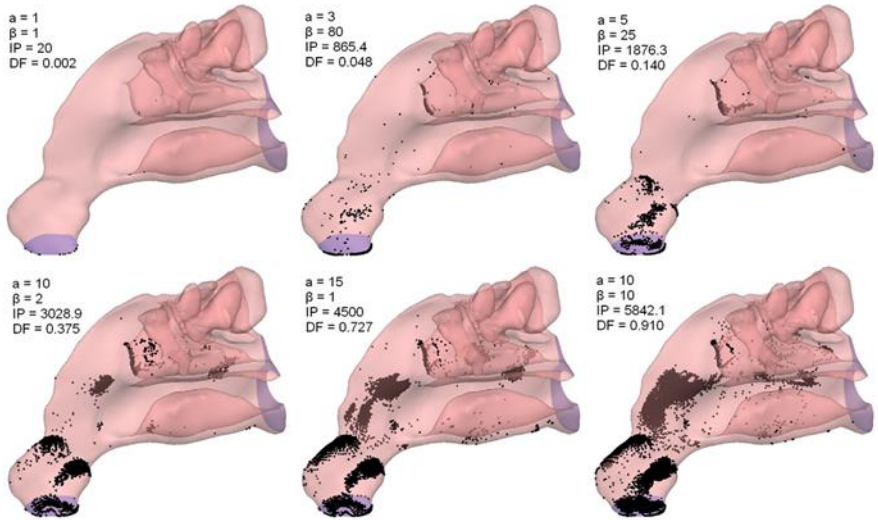


Percent of maximum receptor binding value from PET scan data

Fowler and Volkow. Journal of Toxicology: Clinical Toxicology. 1998;36(3):163-74

Case 3: Computational Fluid Dynamics (CFD) Modeling of NDPs

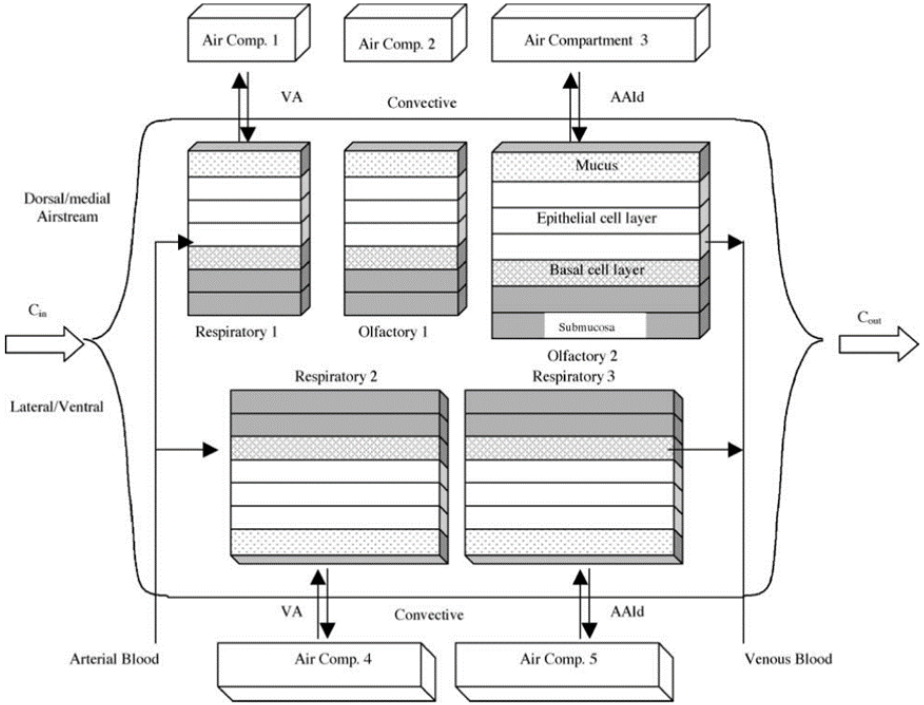
- Predict influence of device and formulation parameters
  - Particle size distribution, spray angle, spray velocity
  - Regional deposition
    - Intersubject variability
  - PK profile
    - Combined with physiologically-based pharmacokinetic (PBPK) modeling



Fiber deposition in nasal cavity, where a is the fiber radius in μm, β is the fiber aspect ratio, IP is the impaction parameter, and DF is the deposition fraction. (Fig. 13 from Dastan et al)

Dastan et al. J Aerosol Sci. 2014;69:132-49

Case 3: PBPK Modeling of NDPs

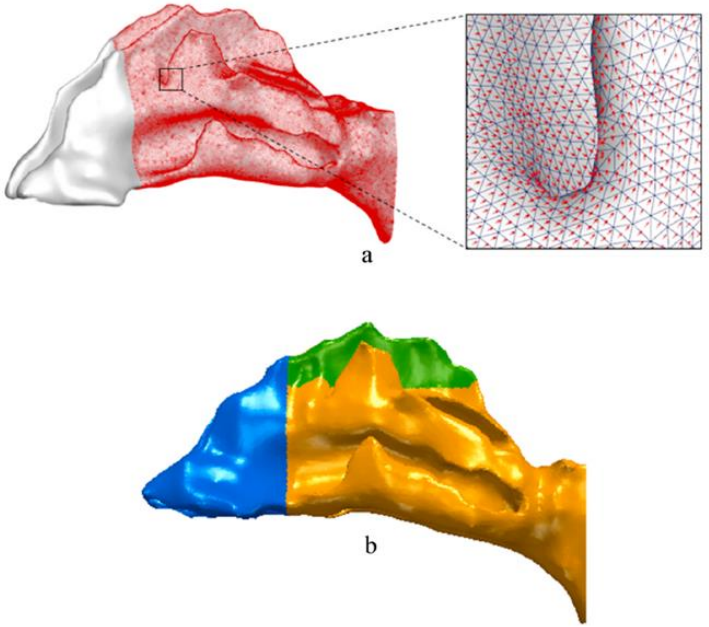


Nasal PBPK model structure as shown in Fig. 2 of Andersen et al.

- Compartmental model
- Prediction of local and systemic PK
  - Dissolution in mucus layer
  - Absorption through nasal tissue
  - Metabolism in nasal tissue
  - Integration with systemic model
- Validated with in vivo PK data

Andersen et al. Regulatory Toxicology and Pharmacology. 2002;36(3):234-45

Case 3: Fully 3D Nasal Mucociliary Clearance (MCC) Model



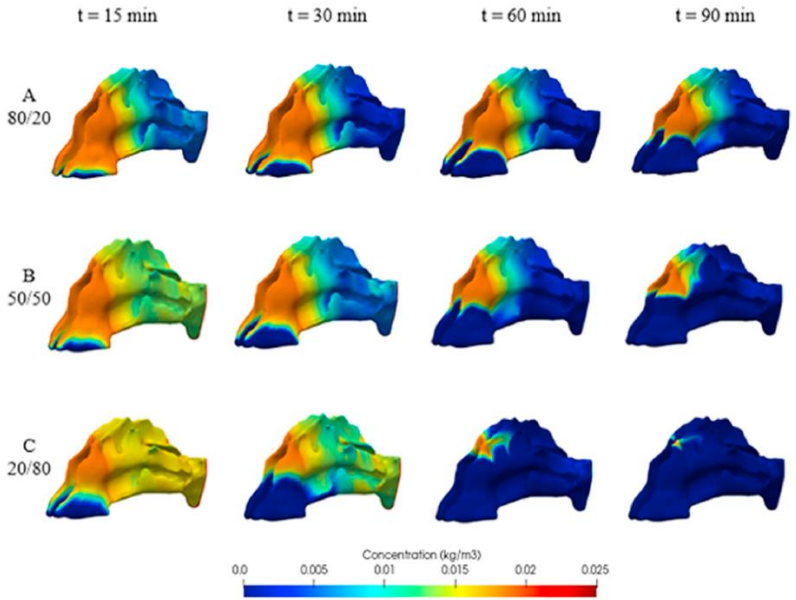
Nasal MCC model features, including a) 6 mm/min mucus velocity vectors in mucus layer and b) regional definitions including olfactory (red), nasal vestibule (blue), and nasal cavity (orange) regions. (Fig. 1 of Chari et al)

- North Carolina State University
  - PI: Clement Kleinstreuer
  - Grant #1U01FD006537: 2018-2021
- 3D CFD model is used to predict regional deposition of NDPs
- Particle deposition locations are directly translated to fully 3D mucus layer model
- Nasal MCC model predicts transit, dissolution, and absorption simultaneously
- Can be used for predicting olfactory region deposition and absorption

Chari et al. Journal of Aerosol Science. 2021;155:105757.

Case 3: Fully 3D Nasal MCC Model – Results

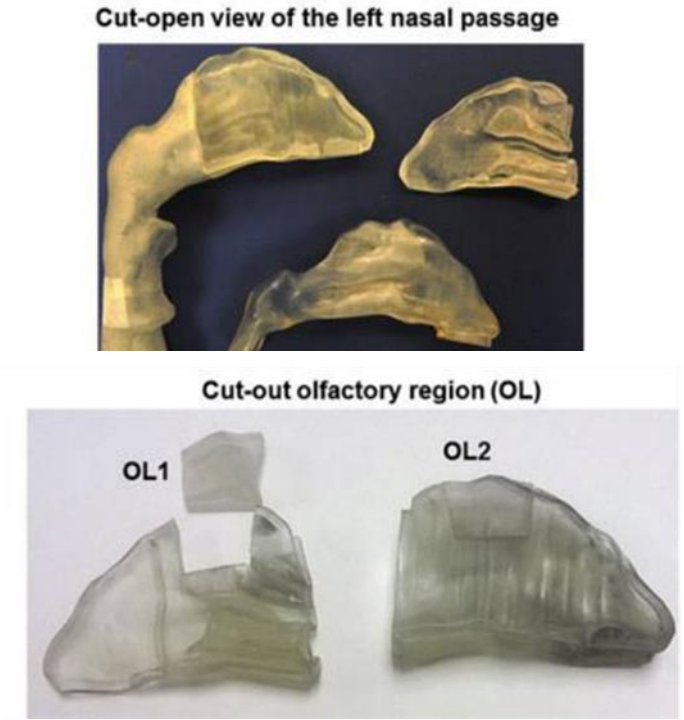
- Model sensitivity was investigated
  - Oil-in-water partition coefficient ($K_{o/w}$)
  - Solubility (C_s)
  - Particle diameter (d)
- High values of $K_{o/w}$ and C_s produced rapid absorption
- Smaller particles show initial burst in absorption rate, but after burst, rates are similar
- Effect of deposition locations was investigated



Mucus layer drug concentrations for drug with $K_{o/w}$ = 0.005, C_s = 0.02 mg/mL, and d = 5 µm for regional depositions ratios in the nasal vestibule and nasal cavity regions of a) 80/20, b) 50/50, and c) 20/80. (Fig. 15 of Chari et al)

Chari et al. Journal of Aerosol Science. 2021;155:105757.

Case 3: Nasal In Vitro Models



Nasal in vitro model that allows for measurement of olfactory region deposition. (Adapted from Fig. 1c of Xi et al.)

- Drug product is actuated into nasal model
- Deposited drug is measured from removable sections using high performance liquid chromatography (HPLC)
- Deposition may show significant intersubject variability according to anatomical differences
- Olfactory deposition may be measured with separate section

Xi et al. Journal of aerosol medicine and pulmonary drug delivery. 2017;30(2):118-31.

Case 3 Summary

1. Nose-to-brain drug delivery is an emerging area for product development.

2. Modeling may be used with relevant in vitro studies to develop an effective toolset to characterize nose-to-brain drug delivery.

3. Further work using PBPK models to address nose-to-brain pathways needed to facilitate their use.

Overall Summary

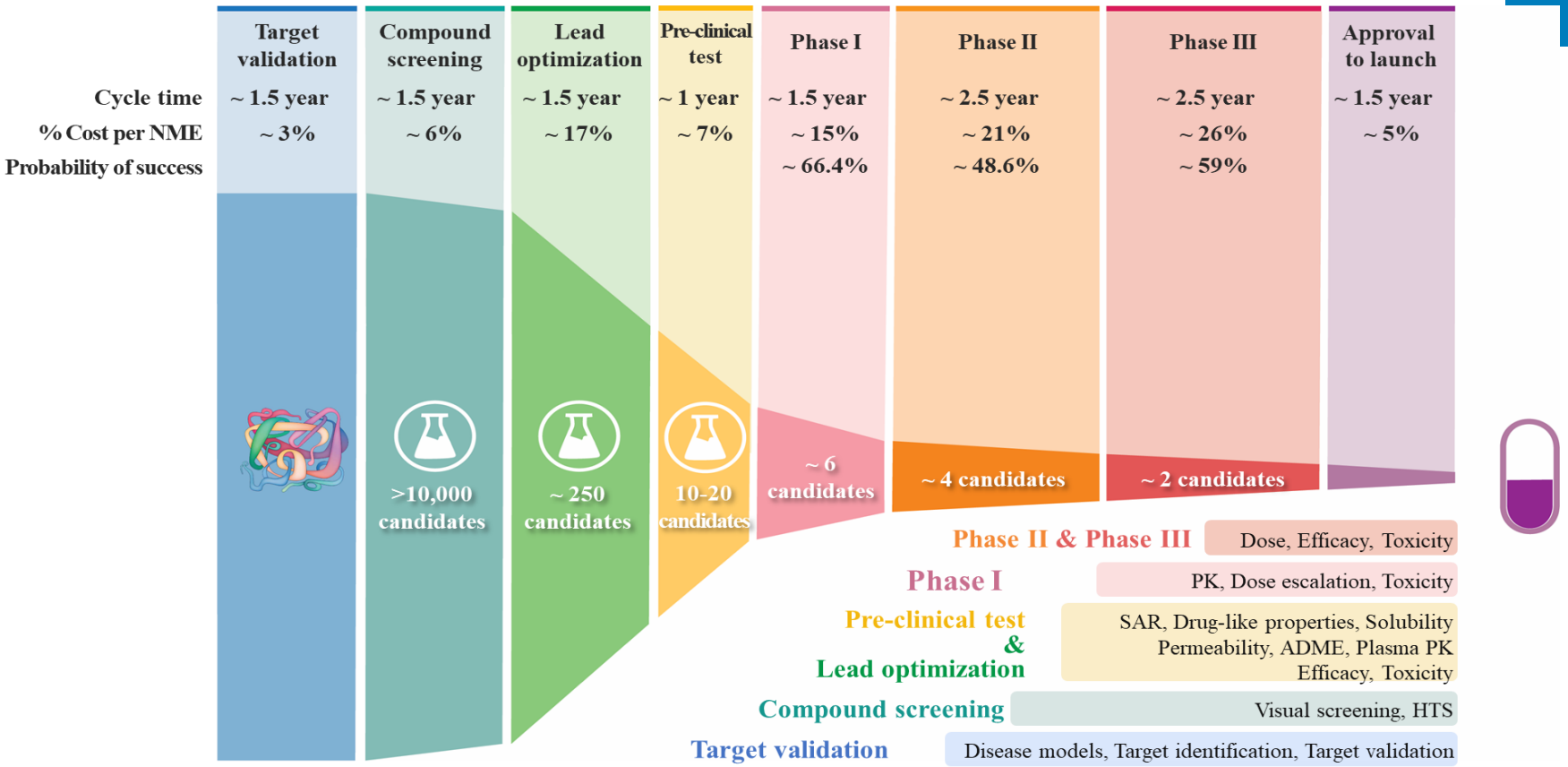
- Unprecedented opportunities for using PBPK models to inform drug delivery and formulation design
- Broadening value proposition of mechanistic modeling from perspectives of drug delivery
- Call for next generation modelers with forward looking vision
  - Post Lewis Sheiner era
  - Go early Go mechanistic!

Acknowledgement

- Case Contributors
  - –Eleftheria Tsakalozou, PhD
  - –Mingliang Tan, PhD
  - –Ross Walenga, PhD
  - –Andrew Babiskin, PhD
  - –Lucy Fang, PhD
  - –All DQMM scientists
- ORS/OGD
  - – Robert Lionberger, PhD
  - – Lei Zhang, PhD

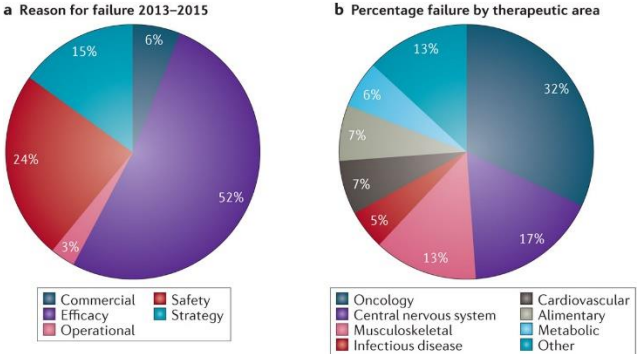
backups

Drug Development Process and Successful Strategies



Slide Adapted from Dr. Duxin Sun

Drug Development Failure Modes (1)



- 40-50%
- 30% -
- 15% -

Lack of efficacy and safety concerns are two main drivers for drug development failure

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Improving the odds of drug development success through human genomics: modelling study

Aroon D. Hingorani[1,2*], Valerie Kuan[1,2,10], Chris Finan[1,2], Felix A. Kruger[3], Anna Gaulton[4], Sandesh Chopade[1,2], Reecha Sofat[2,5], Raymond J. MacAllister[6], John P. Overington[1,7], Harry Hemingway[2,5], Spiros Denaxas[2,5], David Prieto[5,9,10] & Juan Pablo Casas[8]

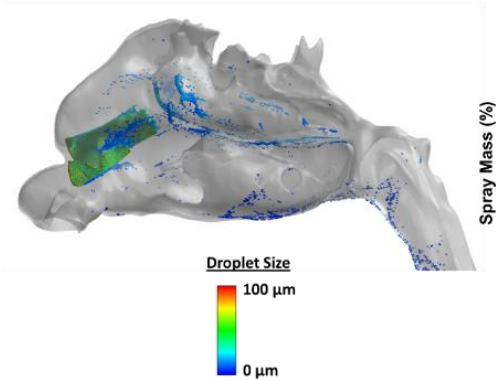
Lack of efficacy in the intended disease indication is the major cause of clinical phase drug development failure. Explanations could include the poor external validity of pre-clinical (cell, tissue, and animal) models of human disease and the high false discovery rate (*FDR*) in preclinical science. *FDR* is related to the proportion of true relationships available for discovery (γ), and the type 1 (false-positive) and type 2 (false negative) error rates of the experiments designed to uncover them. We estimated the *FDR* in preclinical science, its effect on drug development success rates, and improvements expected from use of human genomics rather than preclinical studies as the primary source of evidence for

...ere based on a sample space defined by all human diseases ...mns; and all protein coding genes – 'the protein-coding ...g a matrix of unique gene- (or protein-) disease pairings. ...,000 diseases, 20,000 protein-coding genes, 100 causal ...ing druggable targets, examining the effect of varying ...g assumptions, on the inferences drawn. We estimated γ, ...ween preclinical *FDR* and drug development success rates, and ...s based on human genomics (rather than orthodox preclinical ...-disease pairings was estimated to be causal ($\gamma = 0.005$) giving ...which likely makes a major contribution to the reported drug ...ed success rate was only slightly greater than expected for a ...es for γ back-calculated from reported preclinical and clinical ...o close to the *a priori* estimates. Substituting genome wide ...studies for preclinical studies as the major information source ...ted to reverse the probability of late stage failure because of ...loyed and the ability to interrogate every potential druggable ...tudies conducted at much larger scale, with greater resolution of disease end-points, e.g. by connecting genomics and electronic health record data within healthcare systems has the potential to produce radical improvement in drug development success rate.

Almost all small molecule drugs and bio-therapeutics (such as monoclonal antibodies) act by perturbing the function of proteins. Drug development is therefore predicated on identifying those proteins or 'targets' that both

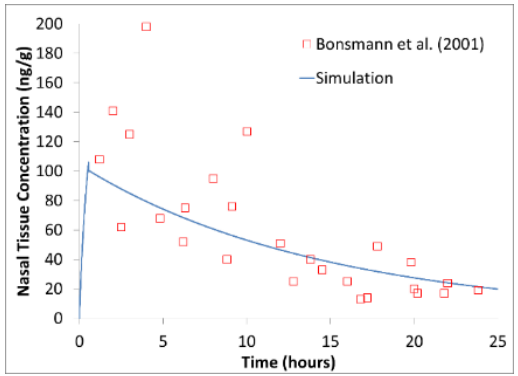
Harrison . Nature Reviews of Drug Discovery, 2016

Hybrid CFD-PBPK for Nasally Inhaled Corticosteroids



CFD predictions for deposition locations of fluticasone propionate droplets, from Kimbell et al.[1]

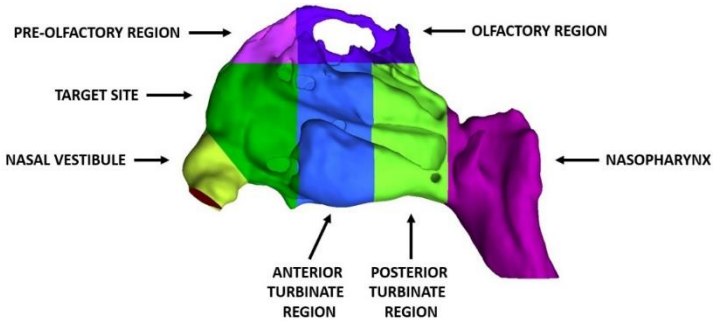
PK predictions of fluticasone propionate nasal spray, from Schroeter et al.[2]



- 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

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[3]

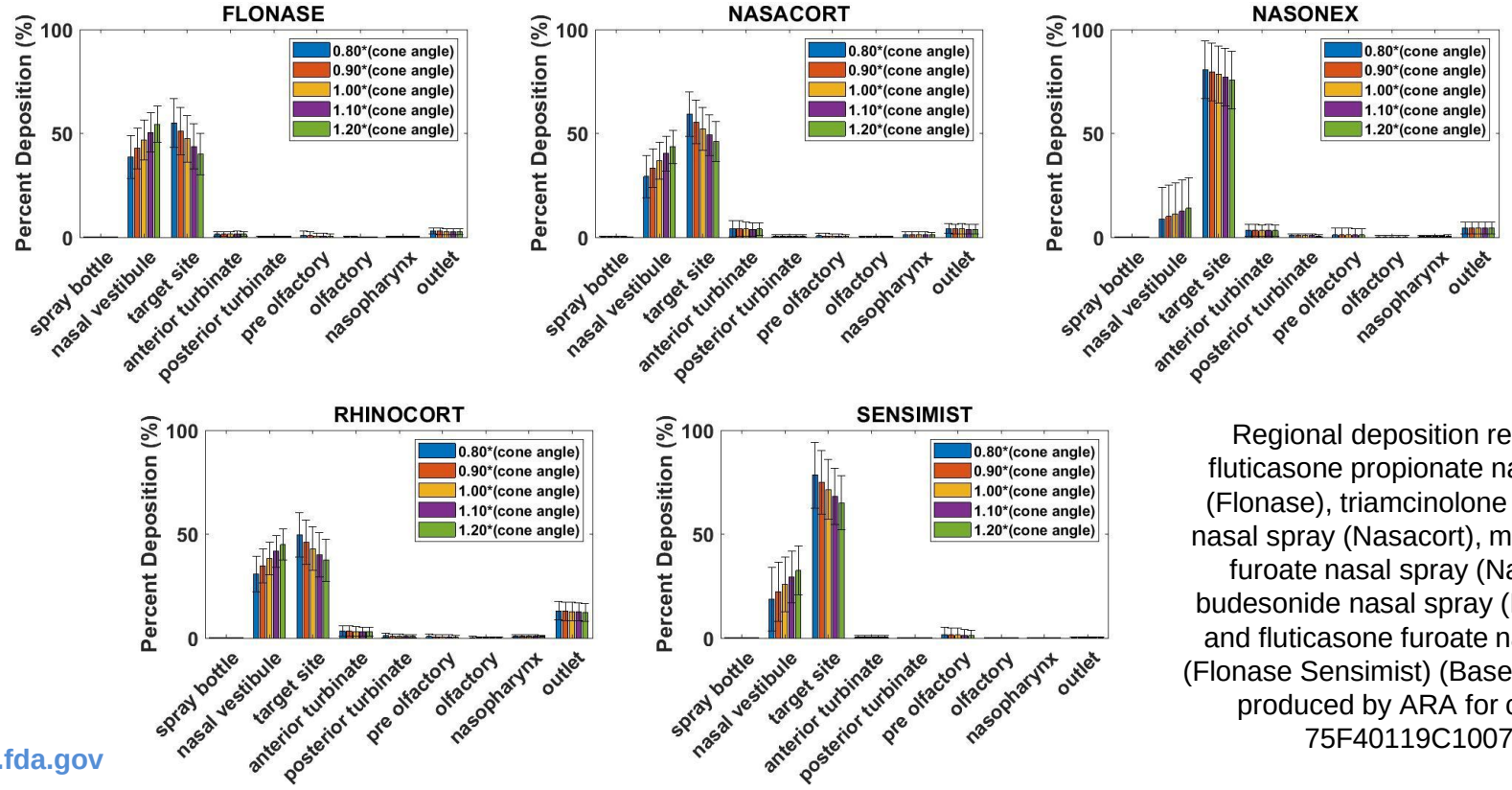
[b] Schroeter et al.[4]

[c] Xi et al.[5]

[d] Hosseini et al.[6]

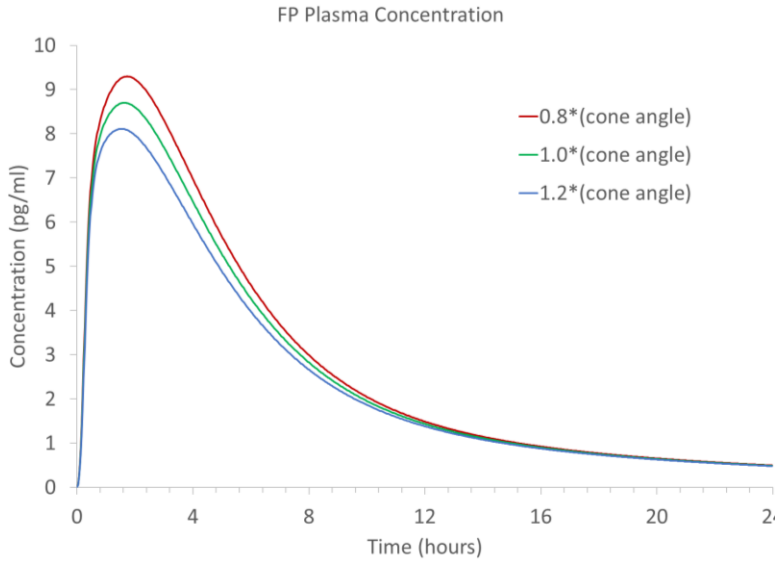
* Estimated valued based on Shrestha et al.[7]

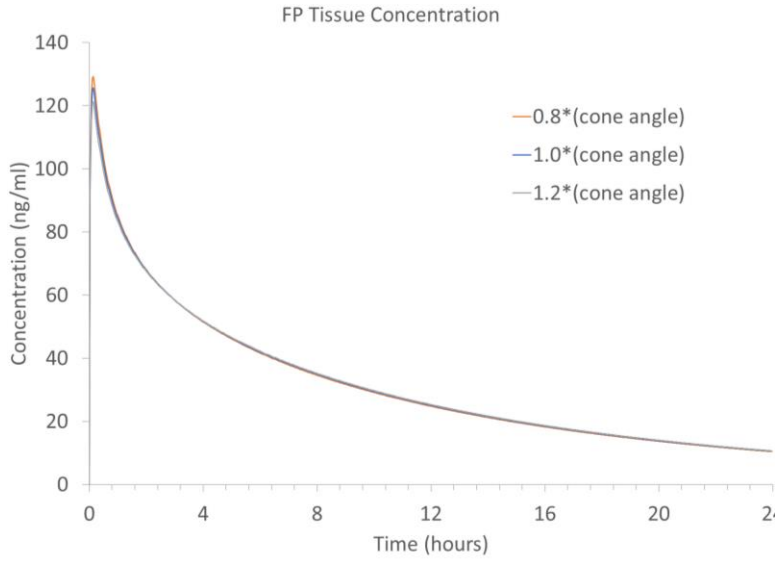
Sensitivity of Regional Deposition to In Vitro Metric Variation



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)

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)

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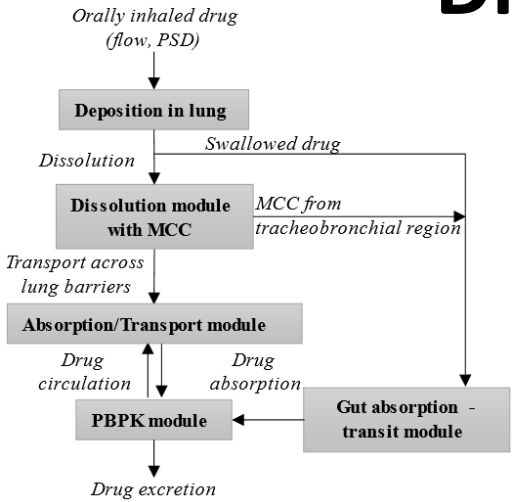
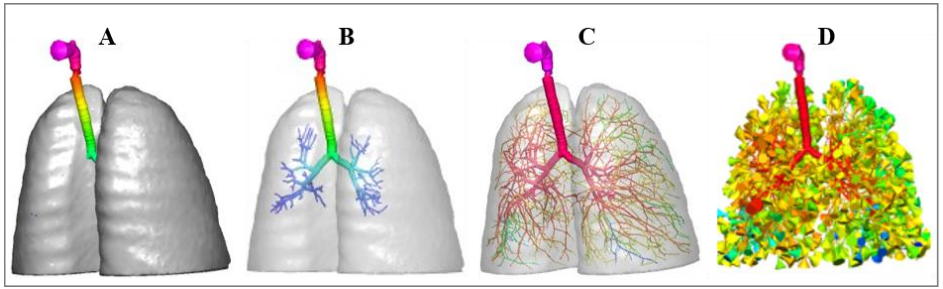
Hybrid CFD-PBPK for Orally Inhaled Drug Products





- CFD Research Corporation
  - Grant #1U01FD005214: 2014-2018
  - Contract #HHSF201810182C: 2018-2022
  - Principal Investigator (PI): Narender Singh
- Quasi-3D computational fluid dynamics (CFD) model predicts deposition and links with Quasi-3D PBPK model for lung absorption
- CFD results serve as inputs to the physiologically based pharmacokinetic (PBPK) model
  - Models are run independently

Figures 1 and 2 from Singh et al.[1]

Quasi-3D PBPK Modeling

- PBPK model simultaneously models dissolution, mucociliary clearance, and absorption on a branch-level basis
- Physiological parameters for each branch depend on location in the lung
  - Tracheobronchial
  - Alveolar
  - Terminal alveolar sacs

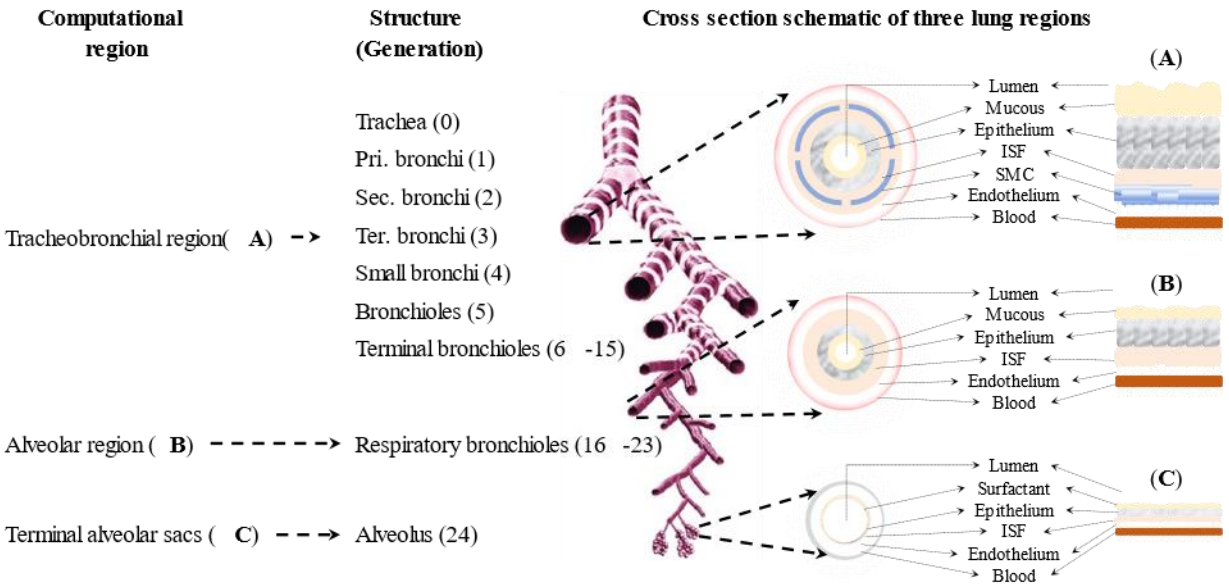


Figure 3 from Singh et al.[1]

Model Validation with Budesonide and Fluticasone Propionate

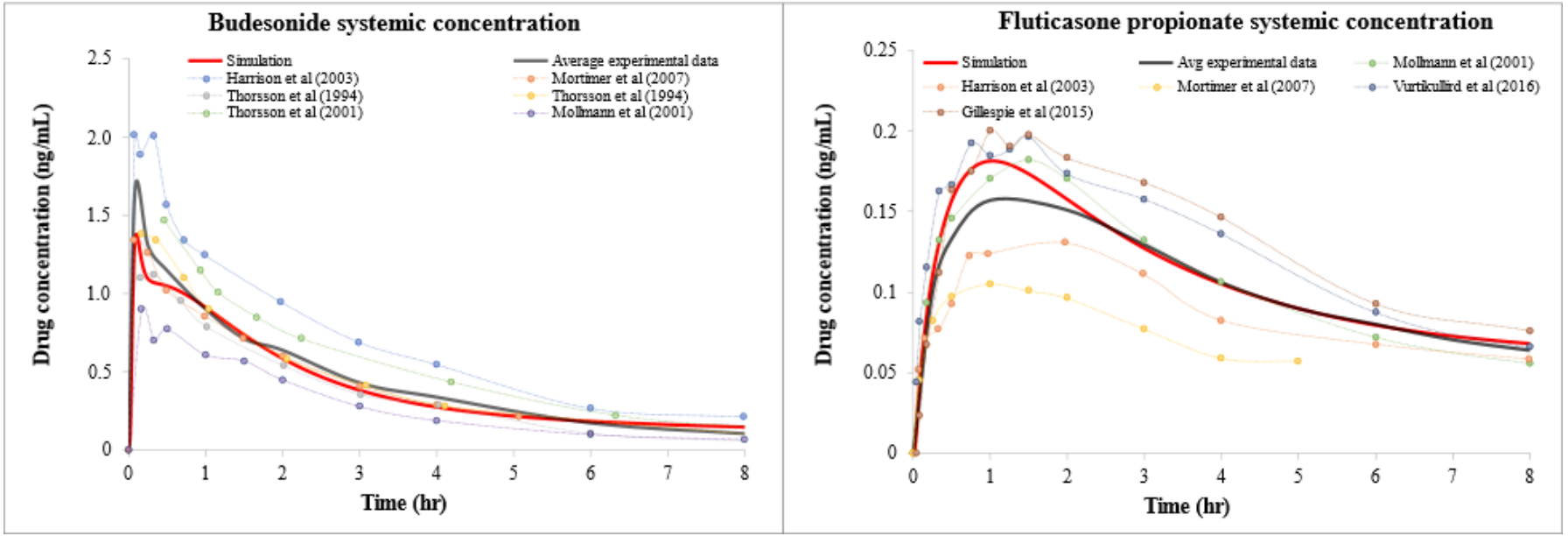


Figure 6 from Singh et al.[1] Model validation for budesonide dry powder inhaler and fluticasone propionate dry powder inhaler as compared with available experimental data (normalized to 1 mg dose).[2-8]

Model Sensitivity with Budesonide

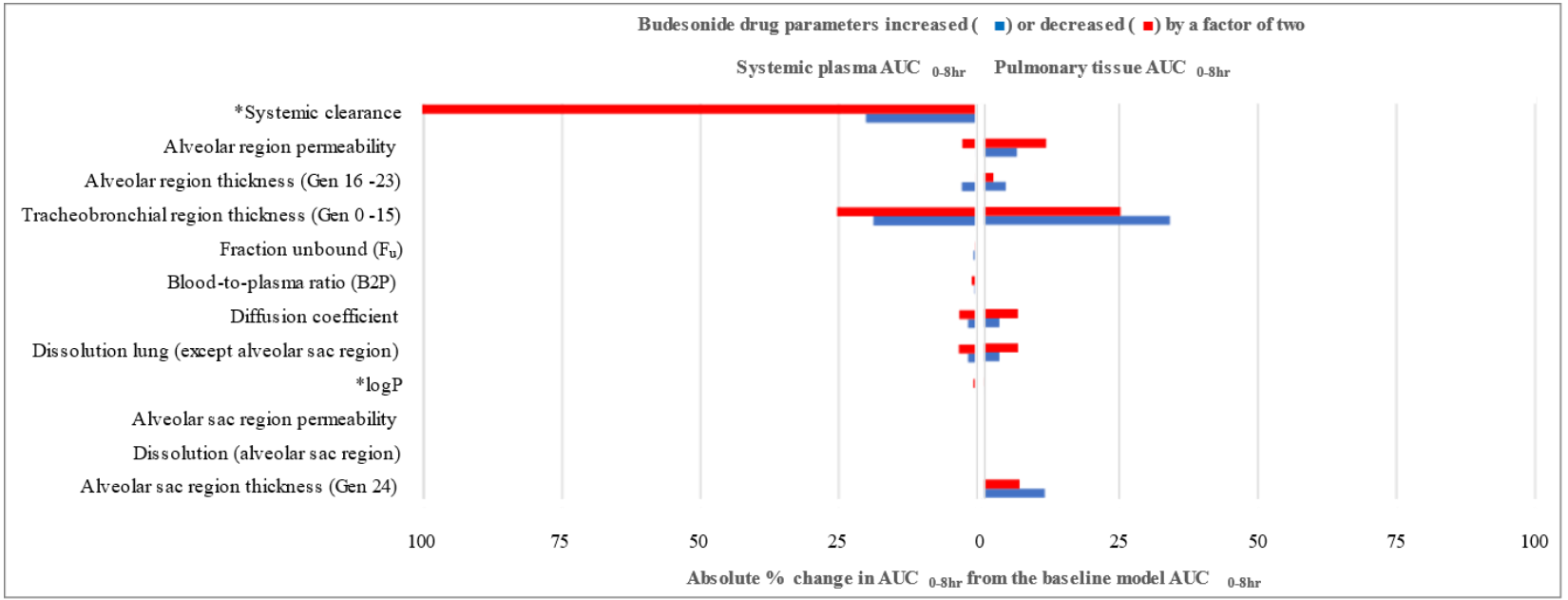


Figure 9 from Singh et al.[1] Model sensitivity analysis for budesonide dry powder inhaler when input parameters are varied by a factor of two. The impact on area under the plasma concentration time curve from time t to 8 hr ($AUC_{0\text{-}8hr}$) is quantified.

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