U.S. FOOD & DRUG ADMINISTRATION

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

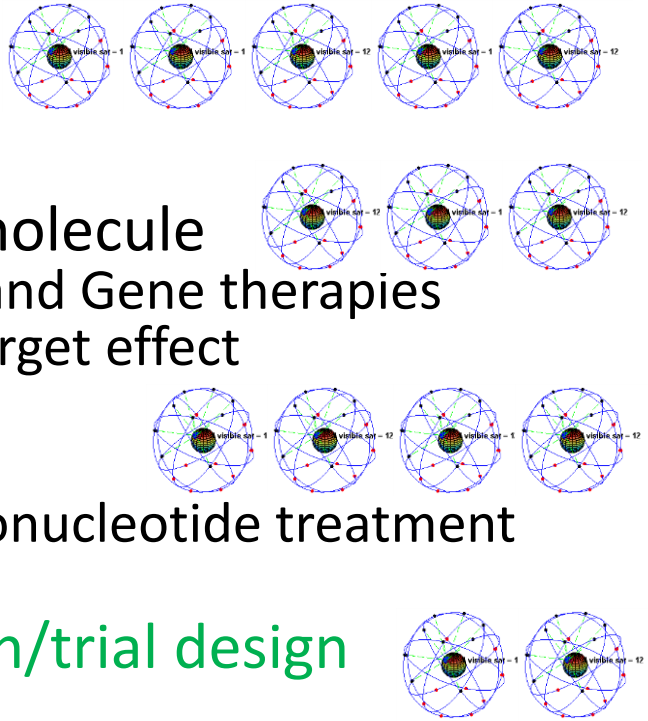
What Are the Drug Development Failure Modes?

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

Development

- Wrong dose/dosing regimen/trial design

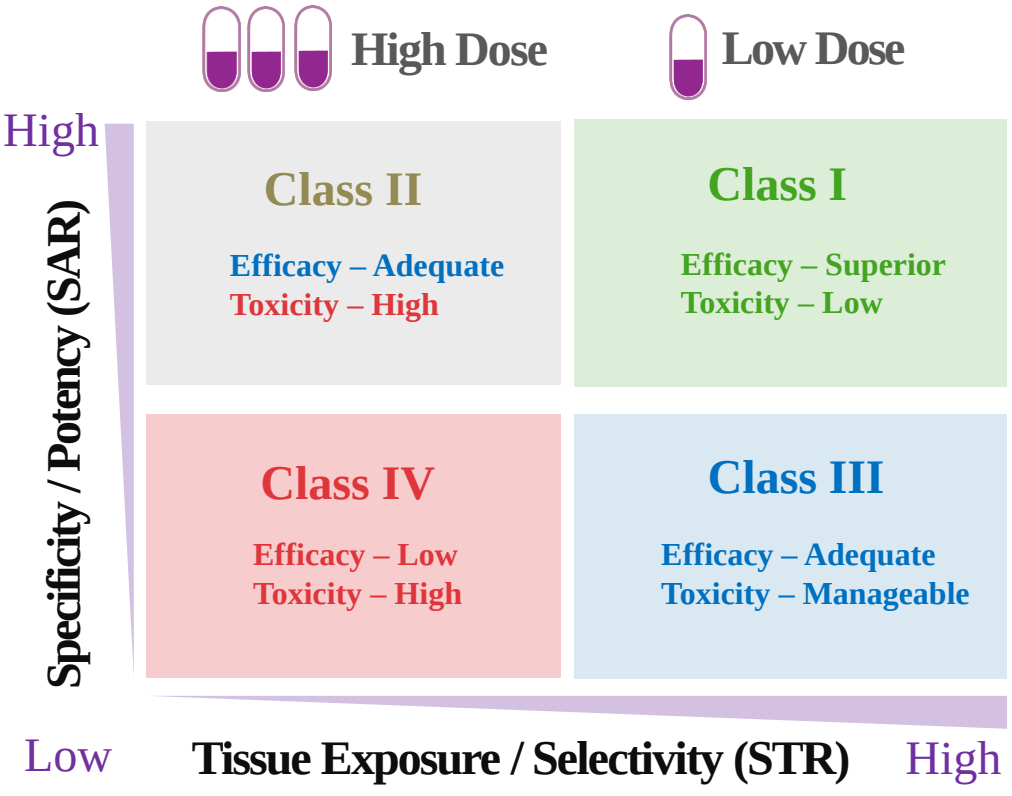


Importance

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

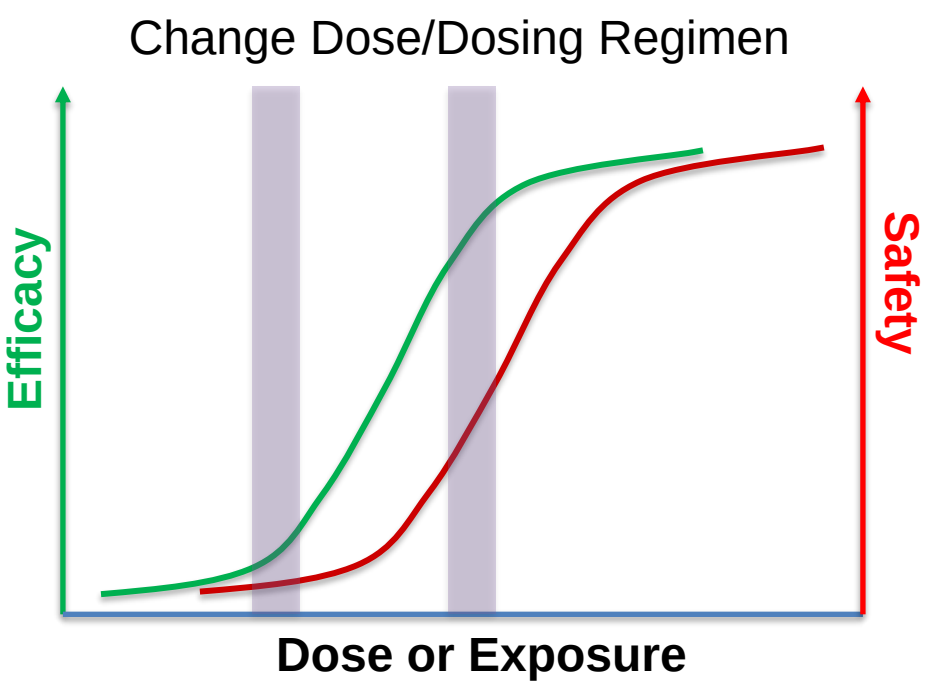


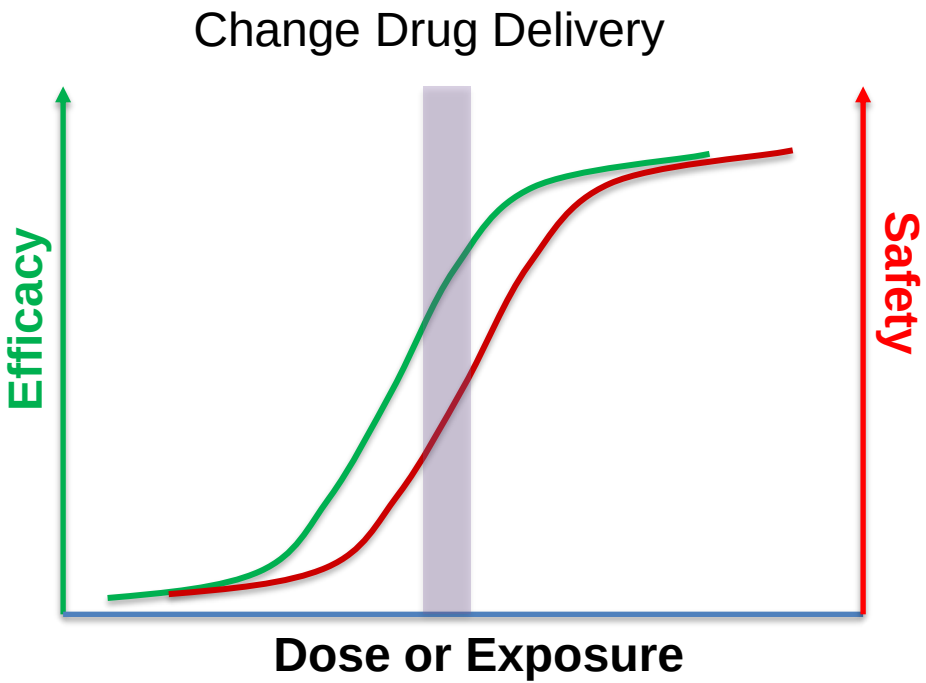
I
Best Success Rate
Most Desirable
Possible Successful Examples:
Viagra, Sofosbuvir, Lipitor, Acalabrutinib, Tamoxifen, Pomalidomide, Propranolol, Famotidine, Clarinex, More

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

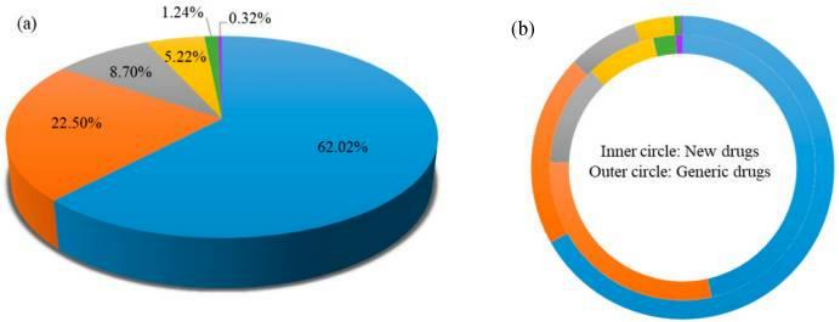
- Oral Absorption
- Orally inhaled
- Intranasal drug delivery
- Ophthalmic
- Topical dermatological
- Female reproductive tract/rectal/otic
- Oligonucleotide delivery (e.g., mRNA)

Concepts behind Complex Drug Products

- Drug delivery systems include **GI Absorption, Inhalation, Intranasal, Topical Dermatological, Ocular/Otic, Transdermal, Intrarectal, Intravaginal/uterine, Parental, Long Acting Injectables, Implantable, Drug Device combiantions etc**

- **Complex Products** Under GDUFA
  - **Complex active ingredients** – Complex mixtures of APIs, polymeric compounds, peptides
  - **Complex formulations** – Liposomes, suspensions, emulsions, gels
  - **Complex routes of delivery** – Locally acting such as dermatological and inhalational drugs
  - **Complex dosage forms** – Long acting injectables and implantables, transdermals, MDIs
  - **Complex drug-device combinations**

FDA-Approved Pharmaceutical Products

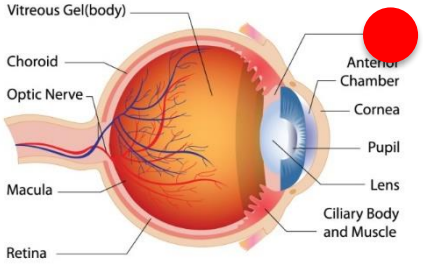


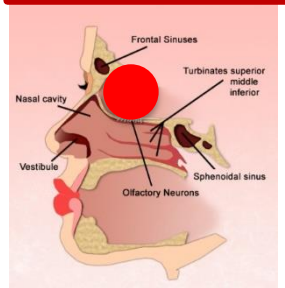
Route	Number (New Drugs)	Number (Generic Drugs)	Ratio	Ranking
Oral	1119	5252	4.69	1
Injection	702	1609	2.29	2
Cutaneous	295	599	2.03	3
Mucosal	205	331	1.61	4
Inhalation	66	61	0.92	5

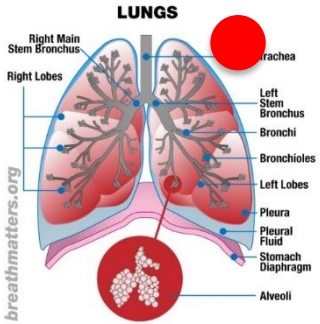
Zhong et al. Pharmaceutics. 2018 Dec; 10(4): 263

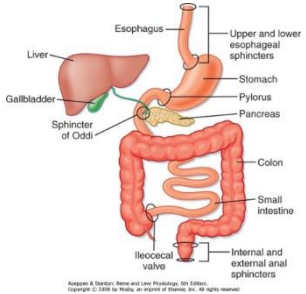
Physiologically Based Models for Drug Delivery

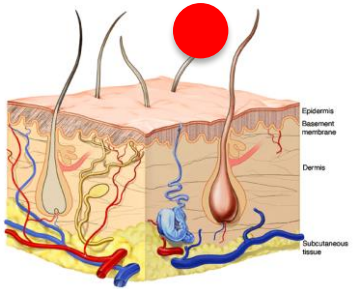
Drug Substance Formulations In Vitro Testing → **Physiological System** → **In Vivo Performance**











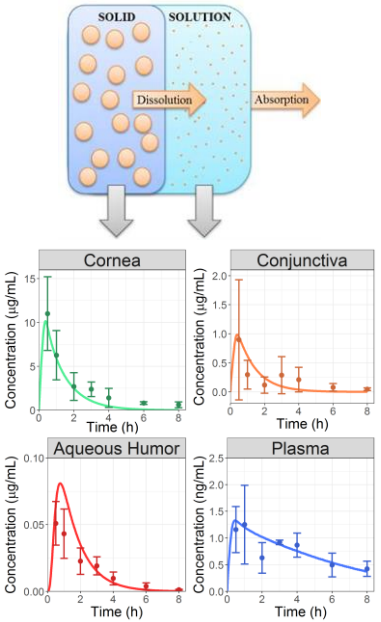
Based on the publication by Jiang W, Kim S, Zhang X, Lionberger RA, Davit BM, Conner DP, Yu LX. Int J Pharm. 2011 Oct 14;418(2):151-60.

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 co-> 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

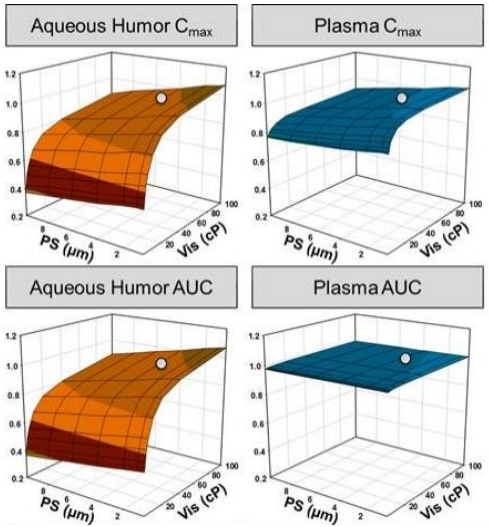


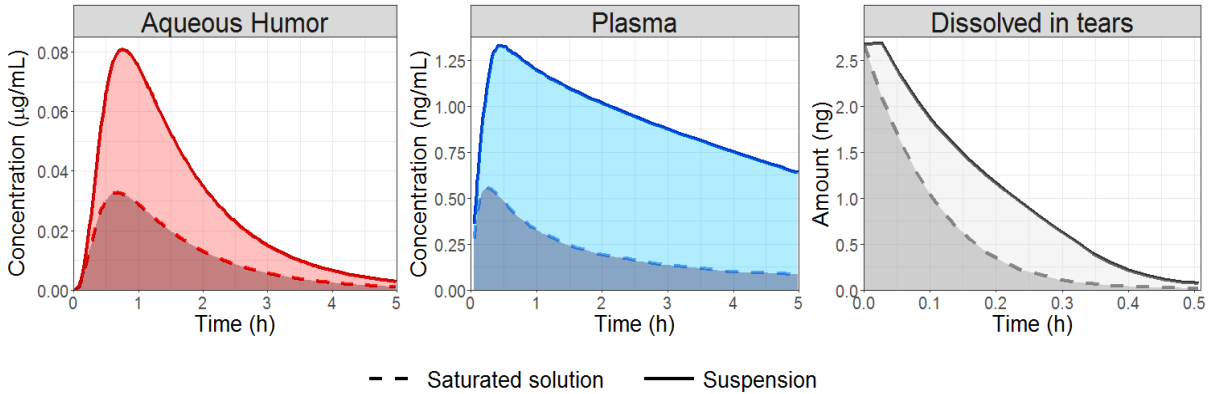
Chockalingam, Ashok, et al. "Protocol for evaluation of topical ophthalmic drug products in different compartments of fresh eye tissues in a rabbit model." Journal of pharmacological and toxicological methods 96 (2019): 9-14.
LeMerdy, Maxime, et al. "Application of Mechanistic Ocular Absorption Modeling 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

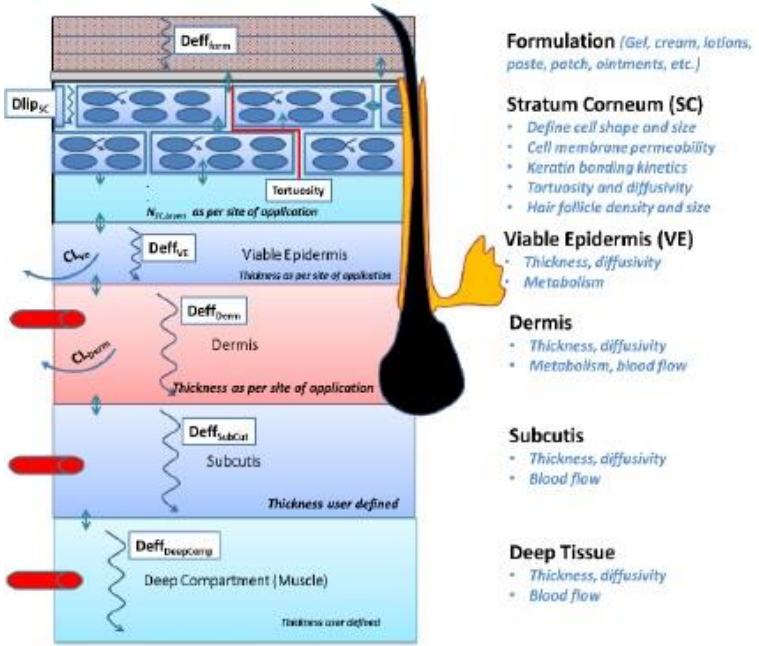
- Solid particles in formulation leads to higher aqueous humor concentrations, BUT …
- Also higher systemic exposure
- A tool for product development that can weigh benefits and risks

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



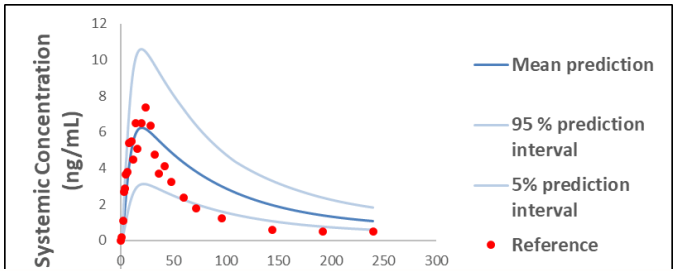
- Diclofenac sodium topical gel, 1%
- Alternative BE approach for a Q1/Q2/Q3 formulation: dermal PBPK model supported alternative to in vivo comparative clinical endpoint BE study
- Model development:
  - API physicochemical properties
  - API ADME properties
  - Formulation attributes for Reference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

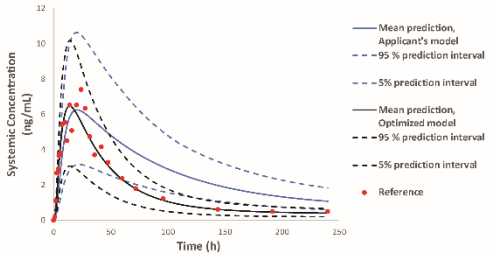
API: active pharmaceutical ingredient; ADME: absorption, distribution, metabolism, and elimination

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





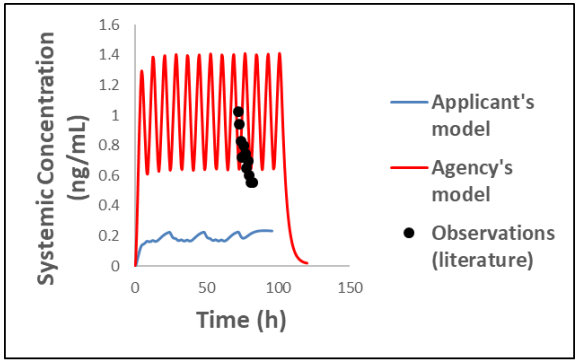
- Platform performance assessment:
  - >10 PBPK models for TDS and topical products
  - Multiple doses/product strengths and dosing regiments
  - Satisfactory model performance
- Model performance assessment for diclofenac sodium topical gel, 1%:
  - Literature and application data on doses, product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

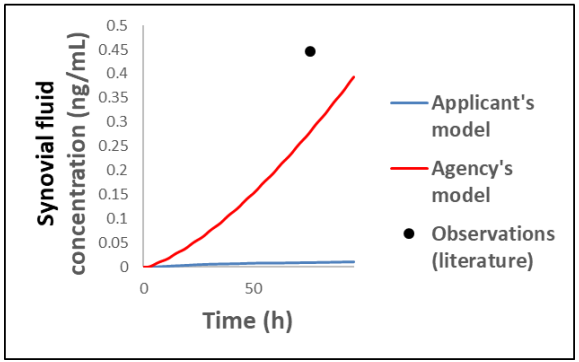
R: Reference, T: Test, TDS: Transdermal Delivery System

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





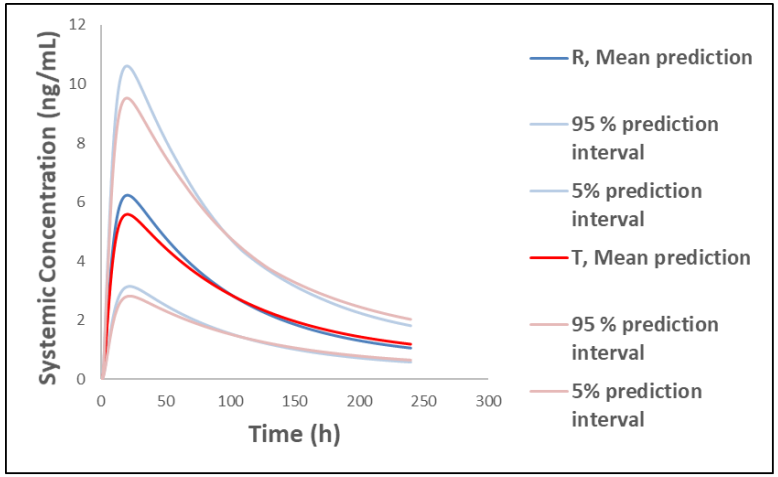
- Refined model to improve synovial fluid exposure predictions (by the Agency)
  - Protein binding in all skin layers
  - Drug product attributes updated
  - Partition coefficients modified leveraging observed local drug amounts

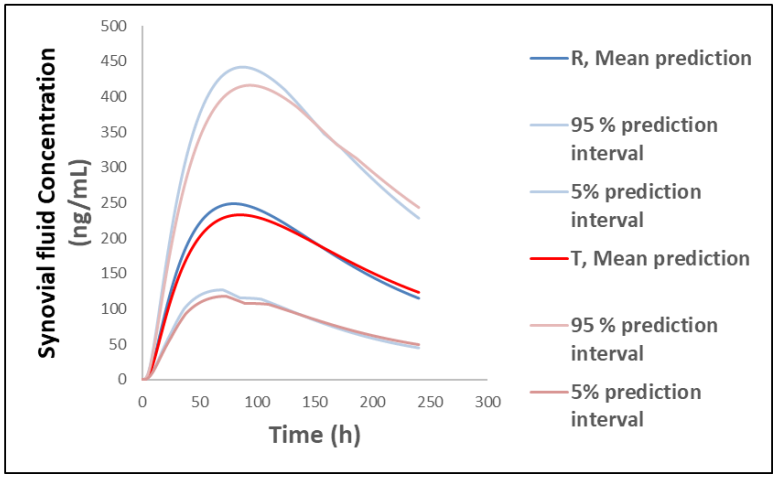
Tsakalozou et al. CPT Pharmacometrics Syst Pharmacol. 2021 Feb 6. doi: 10.1002/psp4.12600

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)

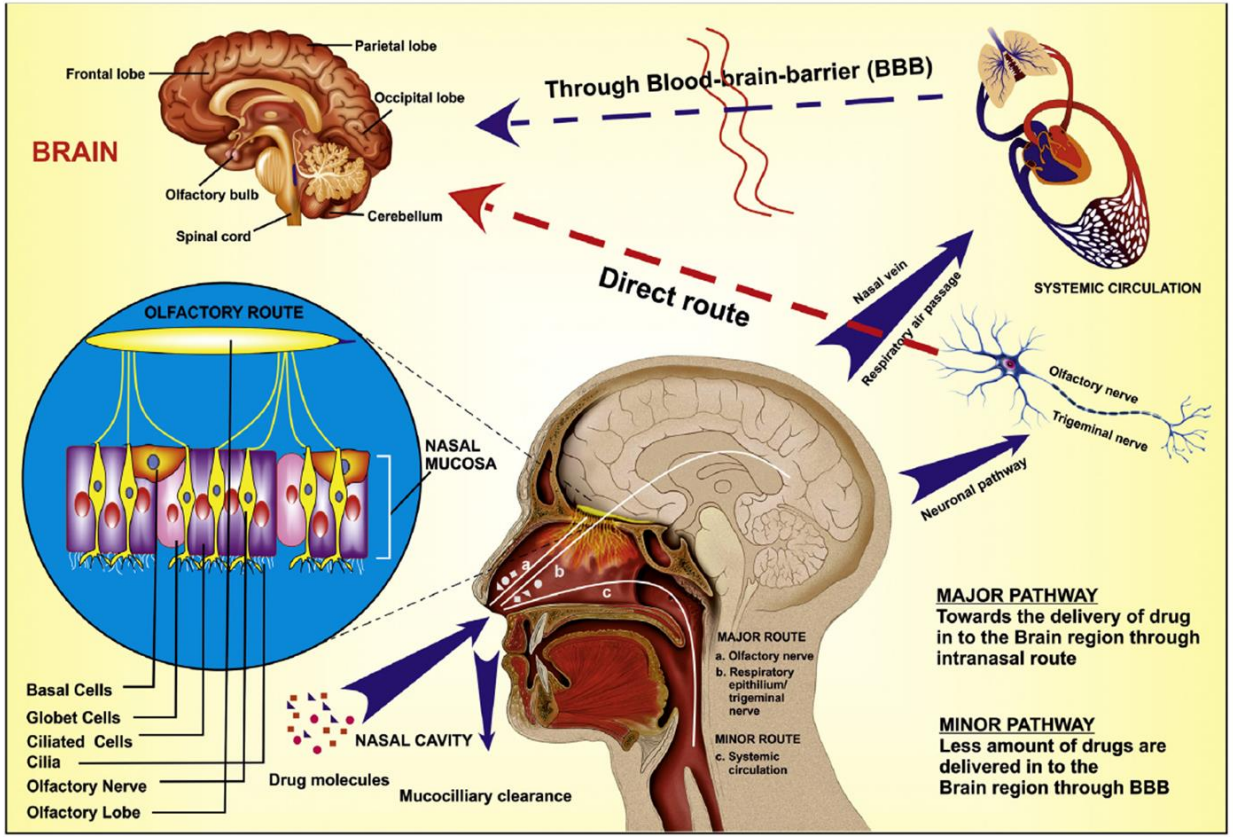
- Treat CNS disorders without the need to overcome the blood-brain-barrier
- Reduce dose needed and possibly increase rate of delivery
- Many treatments are in development
  - Alzheimer's Disease
  - Parkinson's Disease
  - Migraines

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.

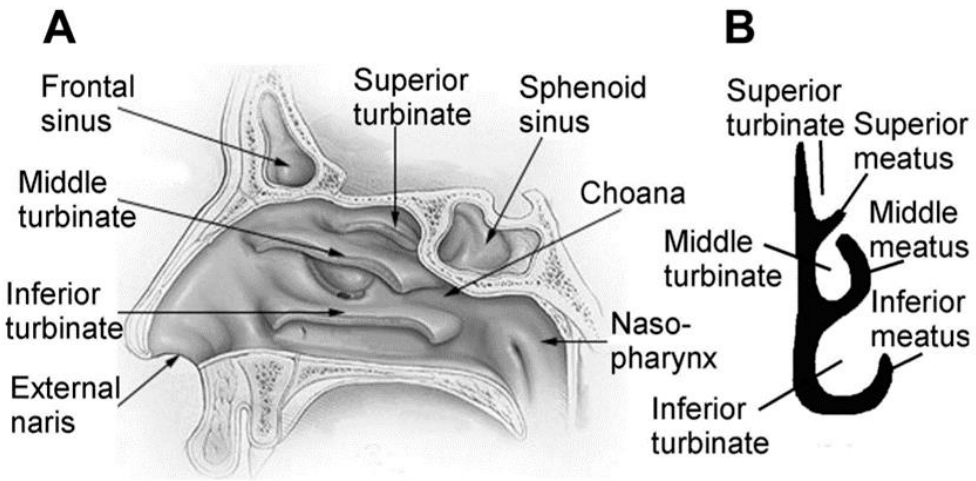
Nose-to-Brain Drug Delivery



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

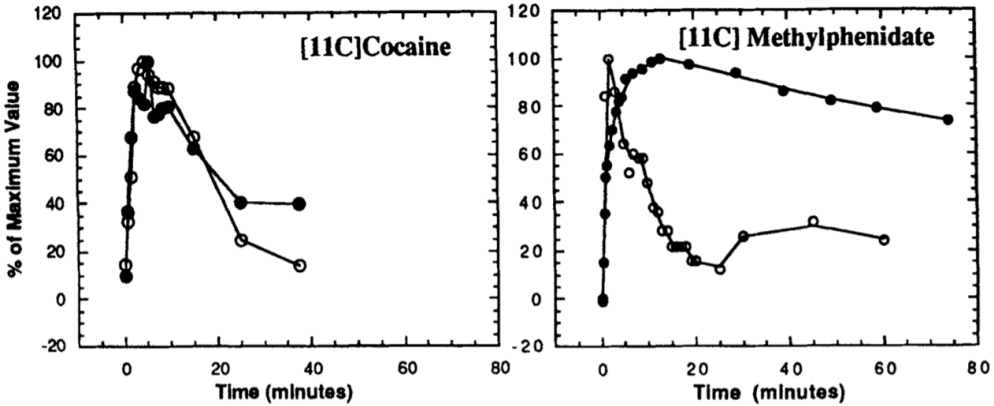
BE recommendations include in vitro studies, in vivo studies, and formulation and device sameness

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?

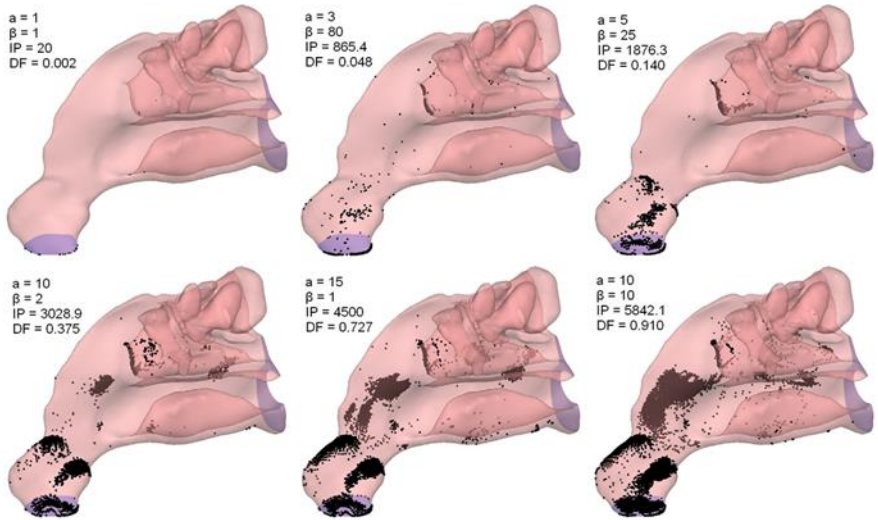


Percent of maximum receptor binding value from PET scan data

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

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

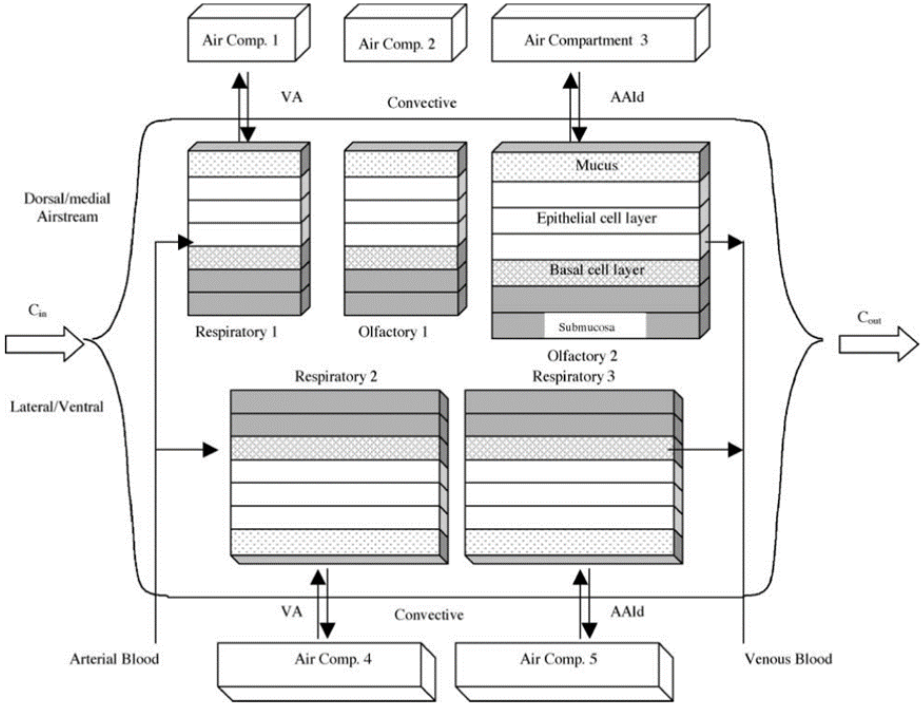
- Predict influence of device and formulation parameters
  - Particle size distribution, spray angle, spray velocity
  - Regional deposition
    - Intersubject variability
  - PK profile
    - Combined with physiologically-based pharmacokinetic (PBPK) modeling



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

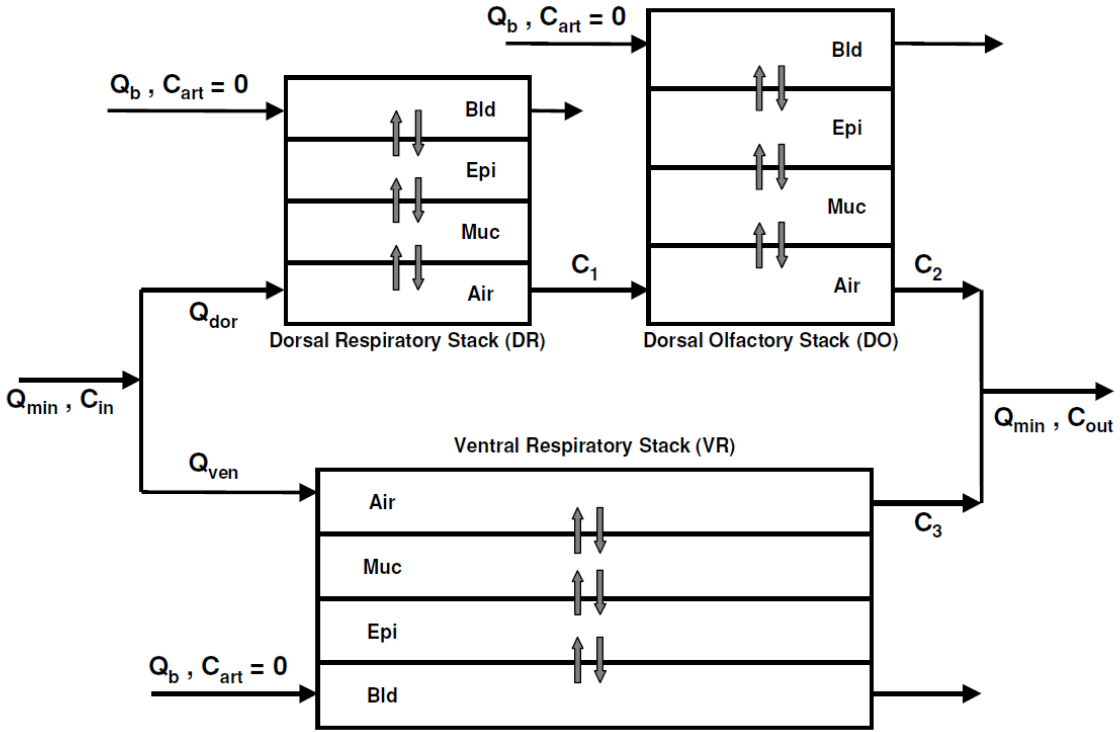


Nasal PBPK model structure as shown in Fig. 2 of Andersen et al.

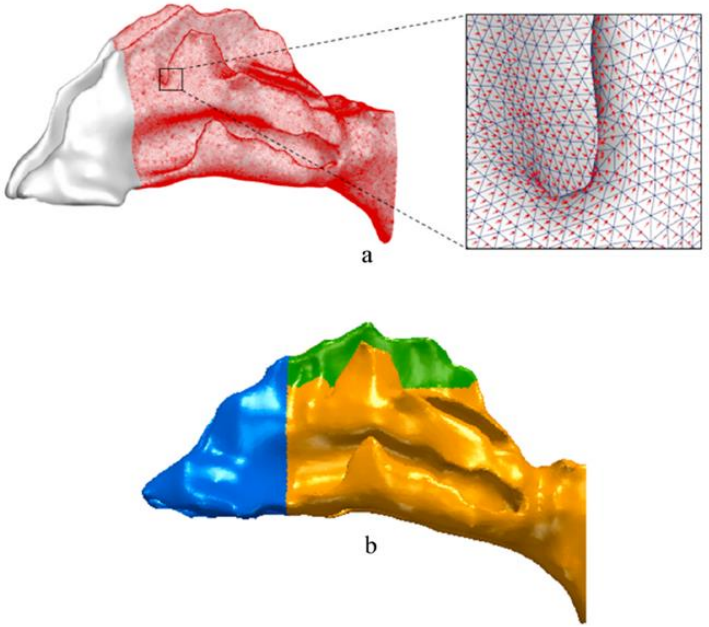
- Compartmental model
- Prediction of local and systemic PK
  - Dissolution in mucus layer
  - Absorption through nasal tissue
  - Metabolism in nasal tissue
  - Integration with systemic model
- Validated with in vivo PK data

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

Modelers' Way to Understand the Scheme



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



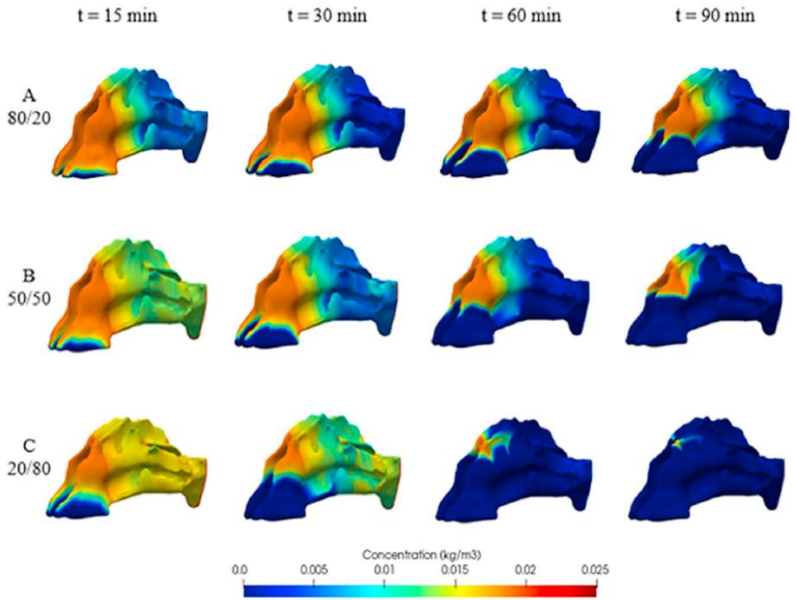
Nasal MCC model features, including a) 6 mm/min mucus velocity vectors in mucus layer and b) regional definitions including olfactory (red), nasal vestibule (blue), and nasal cavity (orange) regions. (Fig. 1 of Chari et al)

- 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

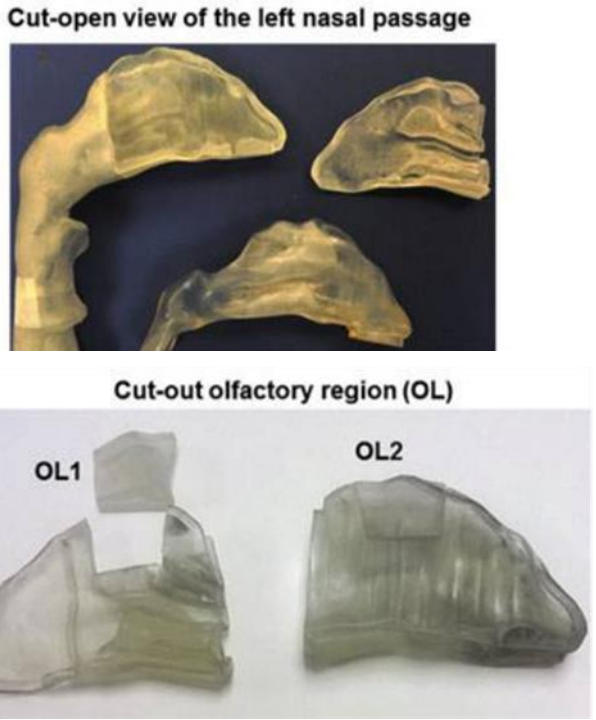
- Model sensitivity was investigated
  - Oil-in-water partition coefficient ($K_{o/w}$)
  - Solubility (C_s)
  - Particle diameter (d)
- High values of $K_{o/w}$ and C_s produced rapid absorption
- Smaller particles show initial burst in absorption rate, but after burst, rates are similar
- Effect of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

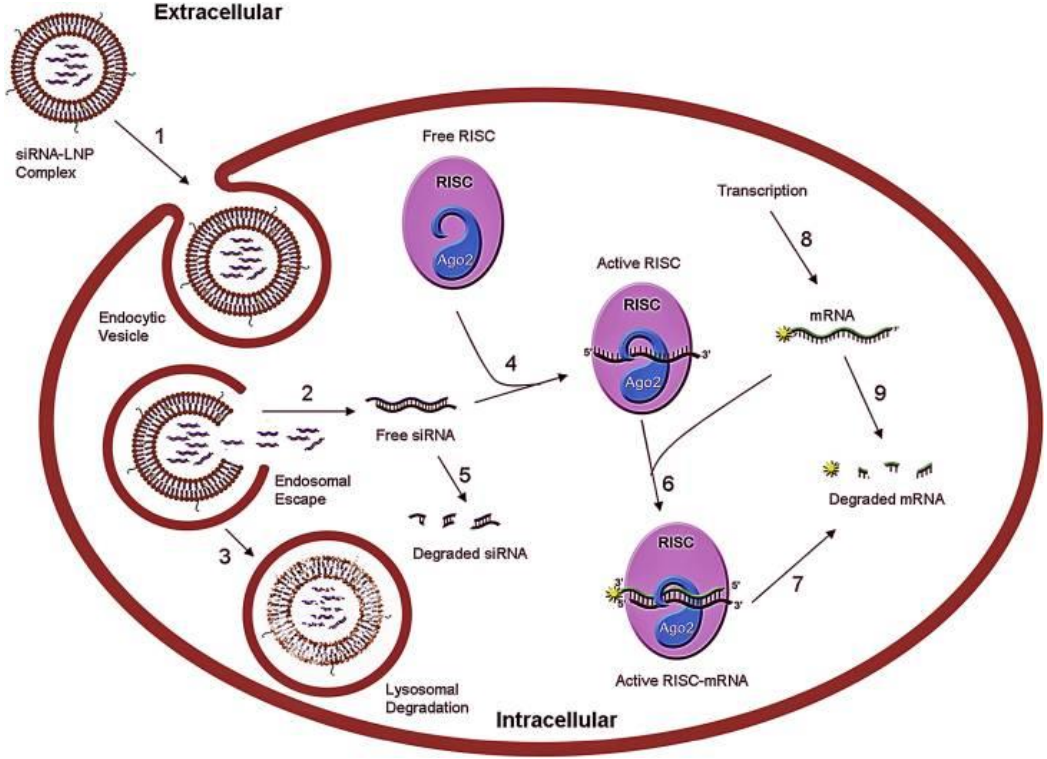
2. Modeling may be used with relevant in vitro studies to develop an effective toolset to characterize nose-to-brain drug delivery.

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

Case 4: Nanoparticles (NPs)

- Drug delivery cannot be determined based on systemic pharmacokinetics (NP properties + tissue properties)
- Multi-scale models to characterize drug distribution at each scale (eg, body, tissue, cellular, and sub-cellular)
  - Endocytosis at cellular level
    - 100-150 nm: Clathrin-mediated endocytosis
    - 50-100 nm: Caveolae-mediated endocytosis is used by smaller NP
    - 40-50 nm: Clathrin- and caveolae-independent endocytosis
  - Other non-receptor or receptor mediated internalization mechanisms
- Model based identification of key factors for NP drug delivery

Case 4: Mathematical Models



$$d[N]/dt = k1 * [E]-(k2 + k3) * [N] \quad \text{(Equation 1)}$$

$$d[S]/dt = k2 * [N]-k5 * [S]-k4 * [S] * [R] \quad \text{(Equation 2)}$$

$$d[SR]/dt = k4 * [S] * [R]-k6 * [M] * [SR] \quad \text{(Equation 3)}$$

$$d[SRM]/dt = k6 * [M] * [SR]-k7 * [SRM] \quad \text{(Equation 4)}$$

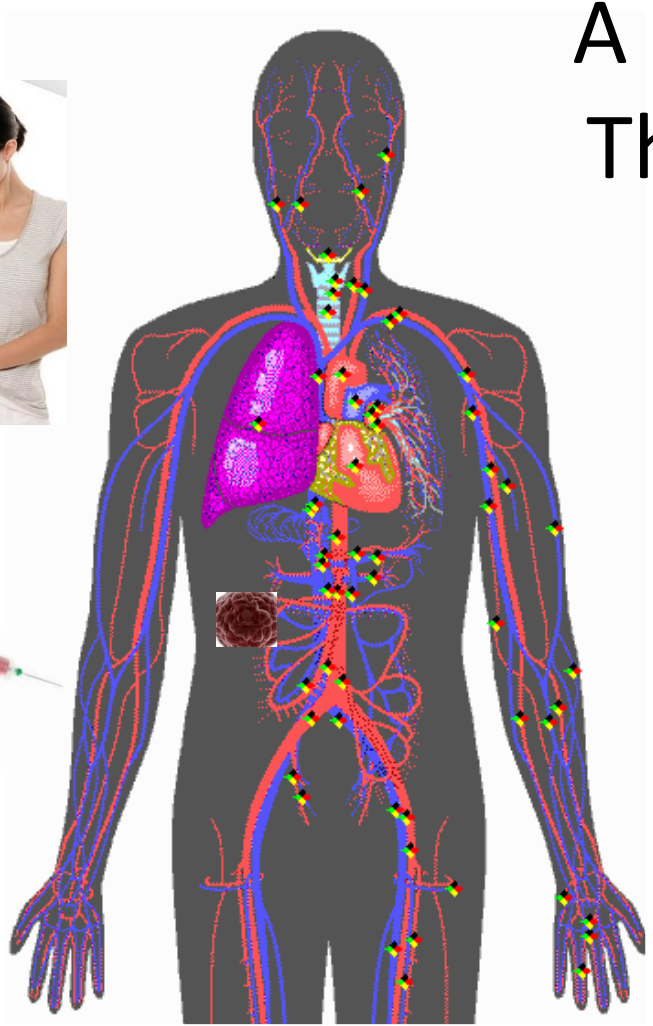
$$d[M]/dt = k8-k9 * [M]-k7 * [SRM]. \quad \text{(Equation 5)}$$

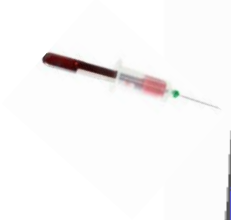
The variables and their initial values used in the above equations are described in Table 1. The model contains nine parameters obtained from direct experimental measurements and published literature,18, 22, 23, 24, 25 as illustrated in Table 1. We modeled these differential equations in the Simbiology toolbox developed for MATLAB users (code is included in the Supplemental Information; The Mathworks).

Case 4: Summary

- Current NP delivery models focus on characterizing what is going on with a formulation but cannot decide what formulation parameter can change delivery
- Future models can be more mechanistic to discover critical quality attributes for NP drug deliveries

A Computational Theory for PBPK





- Route with Tumor Visits
- Route 1
- Route 2
- Route 3

How to mathematically describe this decomposition?

http://www.innerbody.com/image/cardov.html

$P(t)$

Matrix Convolution Expansion in a Linear System

Theorem 1 *In a linear n-compartment system, the probability matrix for a drug molecule to travel from one compartment to another with m inter-compartment transitions after an elapsed time t can be expressed as*

$$\mathbf{P}^m(t) = \left(\left(\mathbf{P}^0 \cdot \mathbf{K}'\right)^{*m} * \mathbf{P}^0\right)(t), \tag{8}$$

*where * is the matrix convolution operator,*

$$\mathbf{K}' = \begin{bmatrix} k_{11} & \cdots & k_{1n} \\ \vdots & \ddots & \vdots \\ k_{n1} & \cdots & k_{nn} \end{bmatrix} - \mathrm{Diag}(k_{11}, \ldots, k_{nn}) = \begin{bmatrix} 0 & \cdots & k_{1n} \\ \vdots & \ddots & \vdots \\ k_{n1} & \cdots & 0 \end{bmatrix}, \tag{9}$$

and

$$\mathbf{P}^0(t) = \mathrm{Diag}\left(e^{k_{11}t}, e^{k_{22}t}, \ldots, e^{k_{nn}(t)}\right). \tag{10}$$

$$\mathbf{P}(t) = \sum_{m=0}^{\infty} \mathbf{P}^m(t) = \sum_{m=1}^{\infty} \left(\left(\mathbf{P}^0 \cdot \mathbf{K}'\right)^{*m} * \mathbf{P}^0\right)(t)$$

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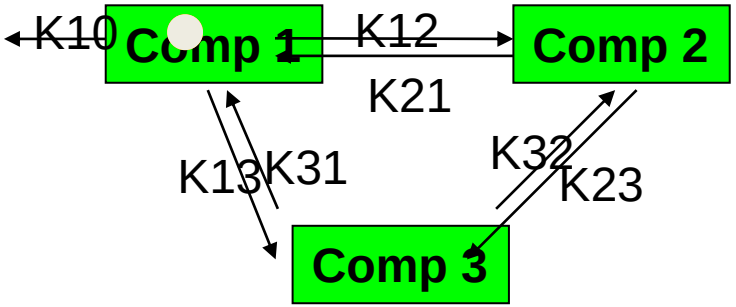
Concept behind the Calculations of a Compartment Model

Probability for a drug to start from comp 1 and end in comp 2 with three inter-compartment transitions after an elapsed time t

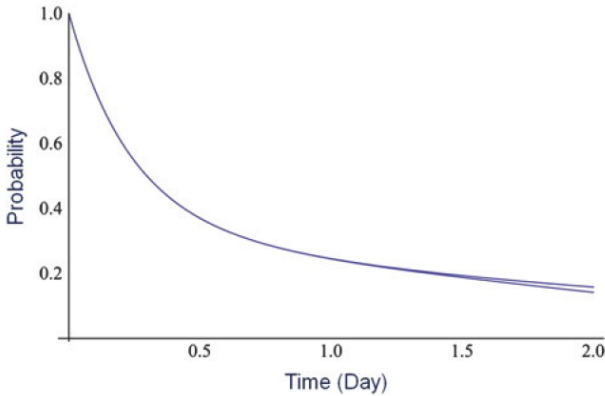


$$P_{12}^{3}(t) = K_{12}K_{21}K_{12}P_{11}^{'}(t)*P_{22}^{'}(t)*P_{11}^{'}(t)*P_{22}^{'}(t)$$
$$+K_{13}K_{31}K_{12}P_{11}^{'}(t)*P_{33}^{'}(t)*P_{11}^{'}(t)*P_{22}^{'}(t)$$
$$+K_{12}K_{23}K_{32}P_{11}^{'}(t)*P_{22}^{'}(t)*P_{33}^{'}(t)*P_{22}^{'}(t)$$

Zhao L. Math Biosci Eng. 2009 Jul;6(3):663-82

Computational Solutions: Conventional Solution vs Matrix Convolution Expansion Method

k12 = 0.75; k13 =1.2; k10 =0.95;
k21 = 3.2; k23 = 1.1;
k31 = 1.2; k32 = 0.6



Solution based on conventional PK method

$$P_{11}(t) = 0.29e^{-5.3t} + 0.37e^{-3.35t} + 0.34e^{-0.38t}$$

Solution based on convolution expansion approach
(only up to 7 inter-compartment transitions are used)

$$P_{11}(t) \approx (-19.35 - 10.30t - 1.20t^2)e^{-4.3t} + (-4.45 - 25.74t + 7.76t^2 - 0.16t^3)e^{-2.9t} + (24.80 - 18.30t + 5.06t^2)e^{-1.8t}.$$

k21+k23=3.2+1.1=4.3
k12+k13+k10 = 0.75+1.2+0.95 =2.9
k31+k32=1.2+0.6=1.8

Significance for fitting?

Utilities of Matrix Convolution Expansion

- Decompose observed drug exposure to summation of drug molecules following all traveling routes
- Can compute target site drug exposure
- Can compute residence times at the target site
- Can compute many other fine details

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 and drug developers with forward looking vision
  - Post Lewis Sheiner era
  - Go early Go mechanistic!

Acknowledgement

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

backups

Case V: Long-Acting Injectable Drug Products

- Long-acting injectable (LAI) drug products are formulated to achieve extended drug release action from days to years when administered via intramuscular, subcutaneous, intravitreal, or other routes.

- These products can help improve patient compliance with a better therapeutic option to treat patients who adhere poorly to frequently administered medication.

Examples of FDA Approved LAI Drug Products and Approved ANDAs

Trade Names	Ingredient	Indication	Dose Frequency	Approved Generic
ABILIFY MAINTENA KIT	ARIPIPRAZOLE	Schizophrenia; bipolar I disorder	Monthly	No
ARISTADA	ARIPIPRAZOLE LAUROXIL	Schizophrenia	Monthly, 6 weeks, 2 months	No
ARISTADA INITIO KIT	ARIPIPRAZOLE LAUROXIL	Schizophrenia	One time	No
SUBLOCADE	BUPRENORPHINE	Opioid use disorder	Monthly	No
PROBUPHINE	BUPRENORPHINE HYDROCHLORIDE	Opioid Dependence	one time (6 months)	No
ATRIDOX	DOXYCYCLINE HYCLATE	Chronic adult periodontitis	1 week	No
BYDUREON BCISE	EXENATIDE	Improve glycemic control in type II diabetes	Weekly	No
BYDUREON...BYDUREON PEN	EXENATIDE SYNTHETIC	Improve glycemic control in type II diabetes	Weekly	No
YUTIQ	FLUOCINOLONE ACETONIDE	Chronic non-infectious uveitis affecting the posterior segment of the eye	36 months (one time)	No
ZOLADEX	GOSERELIN ACETATE	carcinoma of prostate, endometriosis, breast cancer	Monthly (4 weeks)	No
SUSTOL	GRANISETRON	Antiemetics for prevention of acute and delayed nausea and vomiting with chemotherapy	Weekly	No
LUPRON DEPOT...LUPRON DEPOT-PED	LEUPROLIDE ACETATE	Endometriosis, Fibroids, Advanced prostrate cancer; children with central precocious puberty	1,3,4,6 months	No
ELIGARD	LEUPROLIDE ACETATE	Palliative treatment of advanced prostate cancer	1,3,4,6 months	No
LUPANETA PACK	LEUPROLIDE ACETATE; NORETHINDRONE ACETATE	Endometriosis	Monthly	No
DEPO-PROVERA	MEDROXYPROGESTERONE ACETATE	Prevention of Pregnancy	3 months	Yes
DEPO-SUBQ PROVERA 104	MEDROXYPROGESTERONE ACETATE	Prevention of pregnancy, endometriosis-associated pain	3 months	No
SINUVA	MOMETASONE FUROATE	Nasal polyps who had ethmoid surgery	3 months (one time)	No
VIVITROL	NALTREXONE	Alcohol/Opioid Dependence	Monthly (4 weeks)	No
SANDOSTATIN LAR	OCTREOTIDE ACETATE	Acromegaly, Carcinoid Tumors and Vasoactive Intestinal Peptide secreting tumors	Monthly (4 weeks)	No
ZYPREXA RELPREVV	OLANZAPINE PAMOATE	Schizophrenia	2, 4 weeks	No
INVEGA SUSTENNA	PALIPERIDONE PALMITATE	Schizophrenia, schizoaffective disorder, mood stabilizers or antidepressants	Monthly	Yes
INVEGA TRINZA	PALIPERIDONE PALMITATE	Schizophrenia	3 months	No
SIGNIFOR LAR KIT	PASIREOTIDE PAMOATE	Acromegaly, Cushing's Disease	4 weeks	No
PERSERIS KIT	RISPERIDONE	Schizophrenia	Monthly	No
RISPERDAL CONSTA	RISPERIDONE	Schizophrenia, Bipolar I Disorder	2 weeks	No
XYOSTED (AUTOINJECTOR)	TESTOSTERONE ENANTHATE	Testosterone replacement therapy	weekly	No
ZILRETTA	TRIAMCINOLONE ACETONIDE	Osteoarthritis pain of the knee	3 months (one time)	No
TRIPTODUR KIT	TRIPTORELIN PAMOATE	precocious puberty	24 weeks	No
TRELSTAR	TRIPTORELIN PAMOATE	Advanced prostrate cancer	4/12/24 weeks	No

Challenges in LAI Product Development and Lifecycle Management

- Long apparent half-life:
  - Longer time to reach steady state
  - Longer wash out time
  - Longer duration for bioequivalence (BE) studies
  - High drop out rate
  - Not practical to perform a single-dose crossover BE study
- Challenging to propose relevant dosing scenarios, e.g.,
  - Impact of early, delayed or missed doses
  - Switching between formulations

Recent Examples of Population PK-MIE Virtual BE

- Proposals for some oncology/orphan drugs in pre-ANDA meetings
- **Reduced sample size** and shorter duration in vivo PK studies
- MIE framework for LAIs by Uppsala University (GDUFA research)

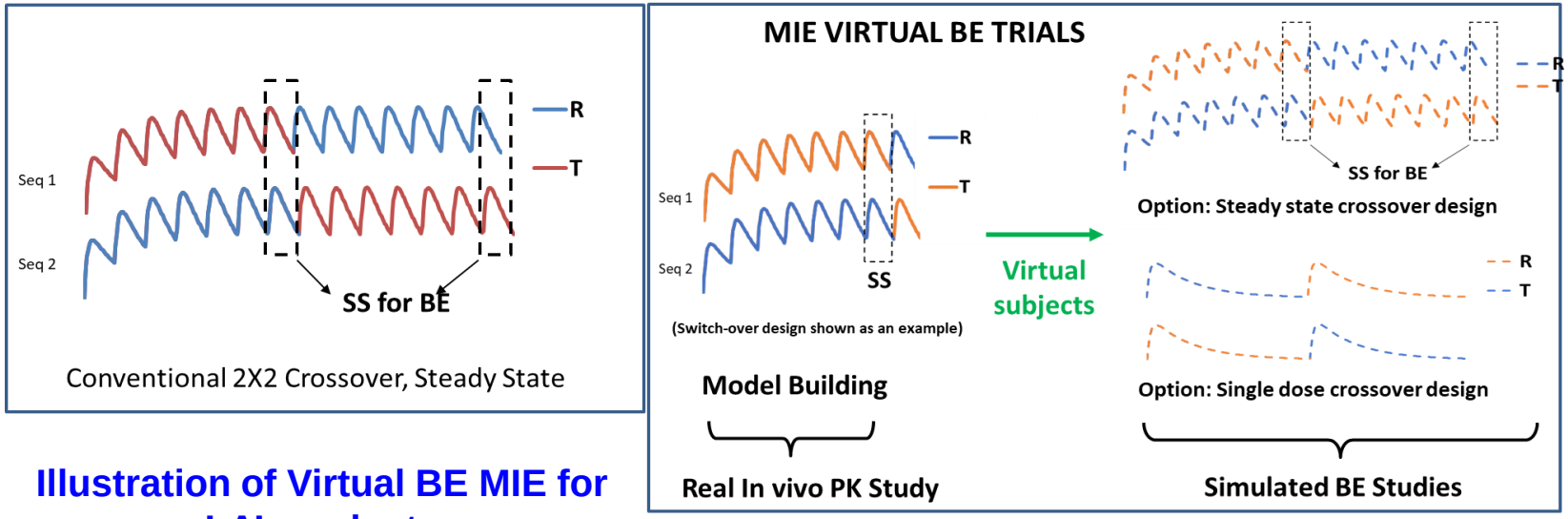

Illustration of Virtual BE MIE for LAI products

Common Deficiencies in MIE VBE

- The applicant did not submit a modeling analysis plan (MAP)
- The applicant did not evaluate the type I error before virtual BE simulation
- The model is not able to detect potential formulation difference between test and reference products
- The sample size of virtual BE simulation is a lot larger than the sample size of clinical BE study for model building without sufficient justifications
- The applicant did not understand that the model building and validation in BE decision is more stringent than the pop-PK modeling in new drug development.

Future Perspectives for LAI

- Further cost saving via
  - Reduction in clinical study size and duration
  - Optimization of study design
- Improving simulation technique
  - Model averaging
  - Non model averaging
  - Bayesian method (Markov Chain Monte Carlo)?
- Model validation
  - Population PK guidance
  - Additional considerations for MIE BE
- Model sharing, submission, communication
  - Model Analysis Plan
  - Model Master Files