FY2018 GDUFA Science and Research Report: Physiologically-Based Absorption and Pharmacokinetic Models for Non-Oral Routes

This section contains only new information from FY2018. For background scientific information and outcomes from previous years on this research topic, please refer to:

- FY2015 GDUFA Science and Research Report: Physiologically-Based Absorption and Pharmacokinetic Models (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm503044.htm)
- FY2016 GDUFA Science and Research Report: Physiologically-Based Absorption and Pharmacokinetic Models (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549175.htm)
- FYs 2013-2017 GDUFA Science and Research Report: Physiologically-Based Absorption and Pharmacokinetic Models for Non-Oral Routes (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm597035.htm)

Introduction

For many drug products that are delivered through non-oral routes, the assessment of bioequivalence (BE) can be challenging as: 1) measurement of drug concentrations at the site of action in humans may not be possible, feasible, or ethical; and 2) systemic drug concentrations can be irreflective of local concentrations, or not measurable at all. FDA is currently advancing through research the development and use of physiologically-based pharmacokinetic (PBPK) modeling for non-oral routes – specifically, orally inhaled, ocular, dermal, and parenteral routes. The overall regulatory goal of this research is to support the use of other indirect methods such as in vitro characterization (e.g., what are the critical quality attributes that control bioavailability) and PK studies (e.g., what metrics on systemic PK ensure equivalent local exposure) that provide a much more sensitive test of equivalence of delivery to the site of action.

Research

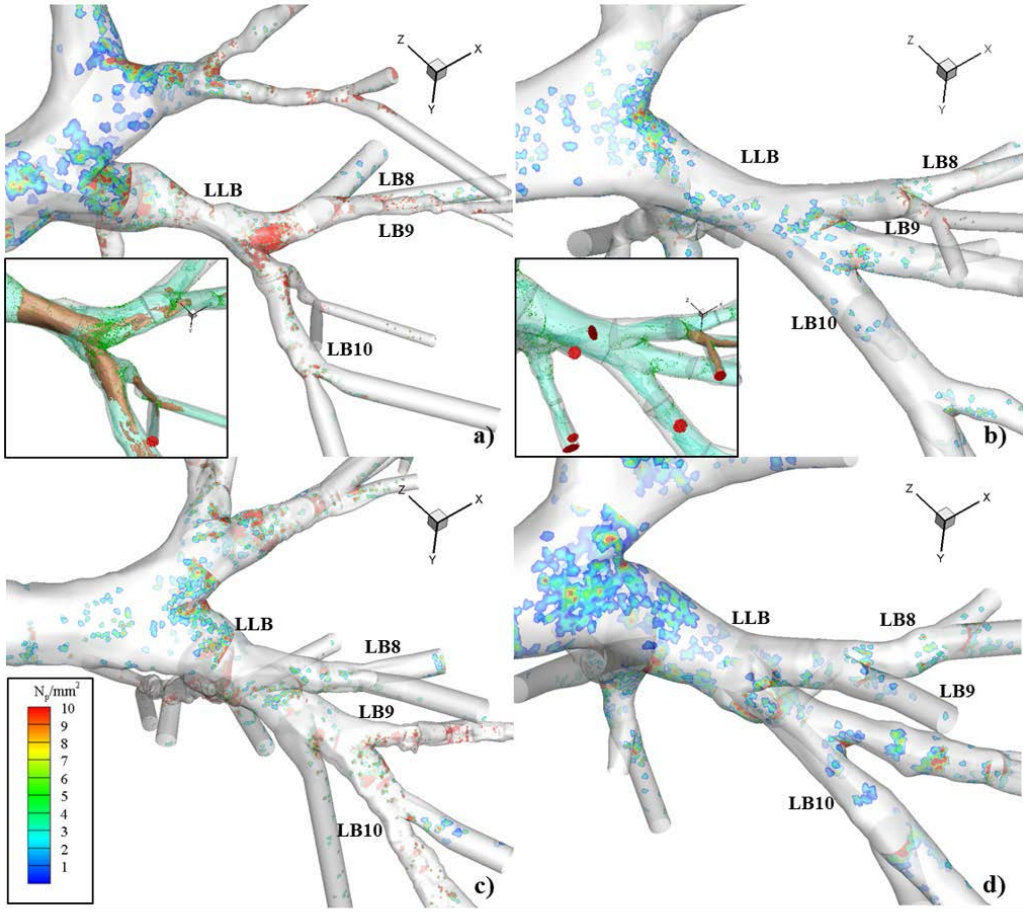
Orally inhaled and nasal

Several external and internal projects were active during FY18 for modeling of orally inhaled and nasal drug products (OINDPs). Grant #1U01FD005201 developed a computational fluid dynamics (CFD) model to predict regional deposition of three brand name inhaled corticosteroid (ICS) drug products in healthy and rhinitic nasal models, as well as to develop a nasal PBPK model to predict absorption, distribution, metabolism, and excretion (ADME). The CFD model predictions indicated that regional intranasal deposition appeared to be most sensitive to disease state and/or intersubject variability, device nozzle insertion depth, and nozzle positioning, while it showed very little sensitivity to actuation force, cone angle, and air flow rate. Grant#1U01FD005214 generated both a CFD and an empirical model to predict regional deposition of OIDPs, as well as a lung PBPK model that was to be coupled to a whole-body PBPK model. CFD predictions of budesonide dry powder inhaler (DPI) drug delivery suggested that the inclusion of cartilaginous rings may have a significant effect of tracheal deposition. In addition to the CFD model, a quasi-3D CFD model was developed which can predict airflow as well as dissolution, absorption, and mucociliary clearance of deposited aerosols. Grant #1U01FD005837 developed CFD models capable of predicting large and small airway deposition of orally inhaled drug products (OIDPs) in healthy subjects and asthmatic patients and included a small clinical study to collect gamma scintigraphy data of inhaled albuterol sulfate in healthy subjects, for validation purposes. To date, six new lung models have been generated, where male and female healthy subject models were created along with four asthmatic patient

models based on division of available computed tomography (CT) scan data into four different clusters. CFD simulations of the new models have shown some significant differences in regional deposition between clusters (**Figure 1**).

As part of Grant #1U01FD005837 and internally, we are focusing on models for the droplets produced by solution-based metered dose inhalers (MDIs). The purpose of this project is to assess the form of deposited aerosols from this product class. A model has been built which includes considerations for droplet evaporation, where preliminary results have shown that nearly all ethanol evaporates prior to exiting the throat. Another internal research project uses CFD to predict regional deposition from "soft mist inhalers," a term that was coined by the brand name manufacturer, Boehringer Ingelheim. These products produce aqueous droplets which may be reasonably expected to stay in solution during inhalation. Product performance will also be evaluated using in vitro testing, including particle image velocimetry and particle size testing. Results from these projects will enhance understanding of the influence of various in vitro measured parameters on regional deposition and help FDA make decisions about BE approaches for solution products.

Figure 1. Particle Deposition Density of 4 µm Particles in the Lower Left Lobe of the a) Cluster 4, b) Healthy Male, c) Cluster 2, and d) Cluster 3 Models.



The inserts in parts a) and b) show air flow speed of 2.5 (green) and 5 (brown m/s). Adapted from Choi J, LeBlanc LJ, Choi S, Haghighi B, Hoffman EA, O'Shaughnessy P, Wenzel SE, Castro M, Fain S, Jarjour N, Schiebler ML, Denlinger L, Lin C-L. *Characteristics of inhaled particle deposition in the lungs of imaging-based asthma*

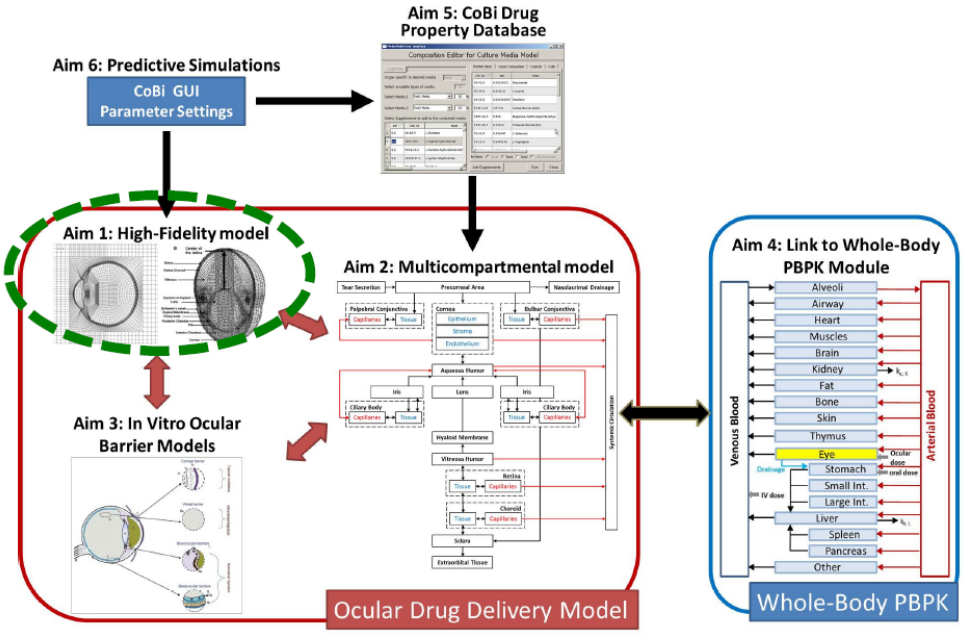
clusters: A numerical study. American Thoracic Society (ATS) 2018 (May 18-23, 2018), San Diego, CA, United States.

Ocular

In September 2014, FDA awarded Grant #1U01FD005211 to Michael Bolger (Simulations Plus, Inc.) to develop the Ocular Compartmental Absorption and Transit (OCAT™) model in GastroPlus™ for ophthalmic suspension formulation and Grant #1U01FD005219 to Kay Sun (CFD Research Corporation) to predict delivery, distribution, and absorption of ophthalmic drug products using a combined CFD and PBPK approach called CoBi (**Figure 2**) in human and animal models. To obtain adequate data for model verification, we initiated an internal project to study dexamethasone distribution in rabbits following ocular administration of a tobramycin/dexamethasone suspension. We successfully developed and verified an OCAT model for dexamethasone and investigated the impact of drug product strength, particle size, particle size distribution and viscosity on in vivo ophthalmic suspension PK performance in rabbits. What we have learned is that the most critical factor influencing the ocular drug bioavailability for ophthalmic suspension is particle clearance through drainage and tears turnover effect in the pre-corneal compartment. The specific drug elimination mechanism in the pre-corneal compartment helps us understand and define drug product specifications.

To enhance our understanding of ophthalmic emulsions, we initiated an internal research project to predict changes in tear break-up time (TBUT) and bioavailability in a patient with keratoconjunctivitis sicca (dry eye disease) based on changes in instilled product viscosity profile as a function of applied shear, surface tension, and osmolality. This project has been completed, and the main result was a parameter sensitivity analysis which demonstrated that model predictions of TBUT and bioavailability were very sensitive to changes in viscosity, while surface tension had a modest effect and osmolality had virtually no effect.

Figure 2. A Multiscale-Multiphysics Computational Tool to Simulate Ocular Delivery, Dissolution, Transport, Absorption and PK.

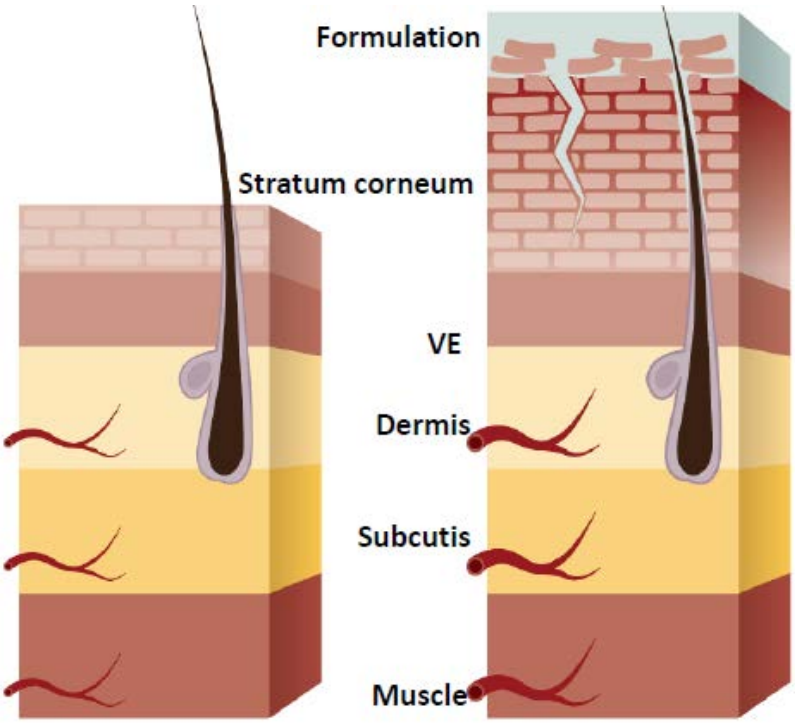


Pre-publication results provided courtesy of Andrzej Przekwas, CFD Research Corporation under the FDA Grant #1U01FD005219: An Integrated Multiscale-Multiphysics Modeling and Simulation of Ocular Drug Delivery with Whole-Body Pharmacokinetic Response.

Dermal

To advance PBPK modeling platforms in the dermatological area, FDA awarded two grants in September 2014. Grant #1U01FD005232 was awarded to Michael Roberts (University of South Australia) to develop PBPK models on dermal absorption of drug products following three different approaches: an analytical solution based on Laplace transformations; a compartmental modeling approach; and a 3D numerical analysis mimicking the geometry of the stratum cornea and processes that occur when a product is applied on the skin. To date, developed in vivo models using Laplace transformations and by employing a compartmental analysis approach were leveraged to simulate skin permeation and corresponding plasma concentration versus time profiles under steady state scenarios (stable flux) of varying diffusion times for slowly and rapidly eliminated compounds. Predictions were obtained when cumulative urinary excretion was modeled as well. Simulations showed that full diffusion and compartmental models behaved similarly. A macroscopic model incorporating formulation attributes (propylene glycol, water content) and skin anatomy information is being developed under the same funding mechanism. Grant#1U01FD005225 was awarded to Sebastian Polak (Simcyp, Ltd.) to develop PBPK modeling and simulation platform for non-gastro-intestinally absorbed drug products in humans with focus on the skin as the formulation application area. Up to now, model advancements through this grant include: updating healthy subject physiology, incorporation of hydration level of stratum corneum and skin pH in different anatomical sites of the body into the model, accounting for the role of skin appendages on absorption, ability to model drug effect on local skin physiology, addition of deep tissue compartment, and development of a psoriasis disease population (**Figure 3**). Incorporation of pediatric and geriatric groups and other ethnic and diseased populations, incorporation of the capability for simulating pharmacodynamic effects and incorporation of empirical models that account for the effect of formulation excipients on drug absorption are ongoing efforts.

Figure 3. Multi-phase Multi-layer (MPML) MechDermal Model Structure in Healthy and Psoriatic Populations.

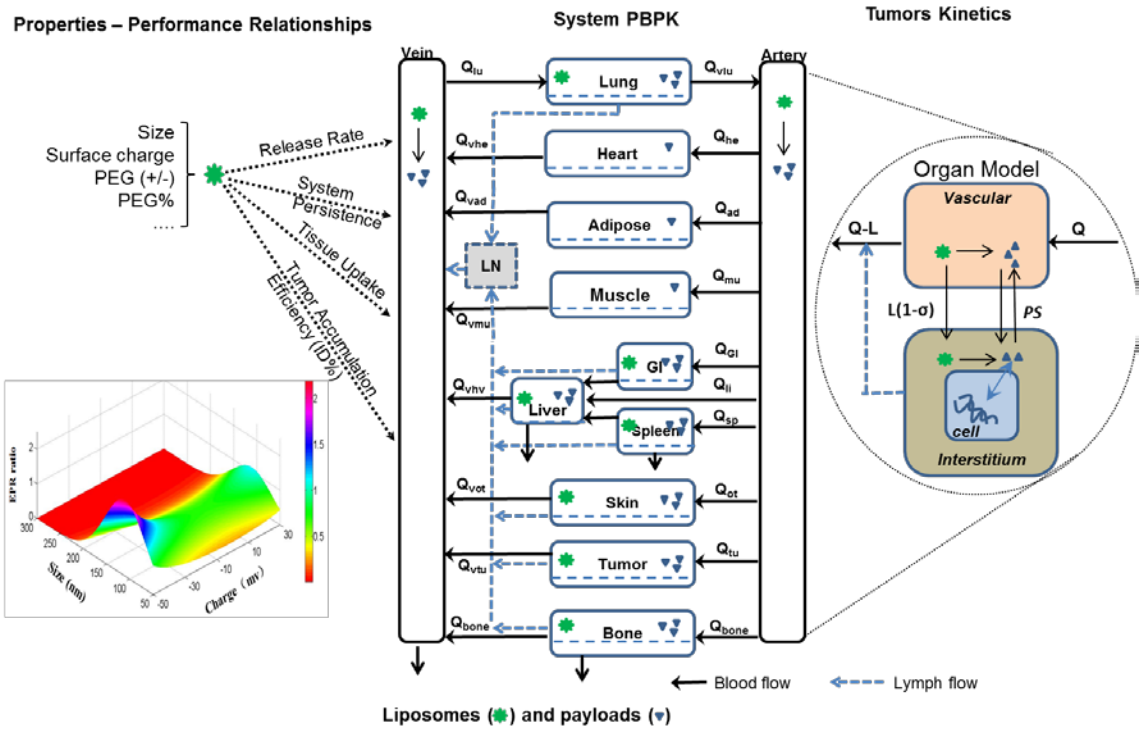


Adapted from Martins FS, Patel N, Jamei M, Polak S. *Mechanistic Physiologically-Based Pharmacokinetic Modeling for prediction of Dermal Absorption in Psoriatic Patients*. Perspective in Percutaneous Penetration, 2018, La Grande Motte, France.

Parenteral

The major purpose of Grant # 1U01FD005206 was to develop a PBPK platform which would be utilized for evaluation of generic versions of liposomal drugs (**Figure 4**). In FY2018, the developed PBPK platform continued to be verified with extensive experimental data from both animals (mouse and rat) and patients in clinical trials. The verified platform was also integrated with quantitative relationships between liposomal drugs physiochemical properties (size, surface charge, and PEG %) and the pharmacokinetics properties (system clearance and tumor distribution). The platform was able to make reasonable predictions of clearance and distributions in xenograft tumors based upon the physiochemical properties of liposomal drugs. Once fully validated, this PBPK platform would show high potential to define the “equivalent characteristic window” for generic liposomal drugs and provide a valuable tool to weigh evidence from in vitro, animals, and clinical studies in regulation of generic liposomal drugs.

Figure 4. The Developed PBPK Platform for Liposomal Drugs and its Integrated Translation from Liposome Physiochemical Properties (Size, Surface Charge, and PEG %) to the In Vivo Performance (Clearance and Tumor Distribution).



Pre-publication results provided courtesy of Yanguang Cao, University of North Carolina under FDA Grant #1U01FD005206: Physiologically Based Pharmacokinetic Model for Drugs Encapsulated into Liposomes.

Research Projects and Collaborations

New Grants and Contracts

- New Contract (HHSF223201810151C) *An Integrated Multiscale-Multiphysics Modeling Framework for Evaluation of Generic Ophthalmic Drug Products* with Andrzej Przekwas at CFD Research Corporation
- New Contract (HHSF223201810255P) *Simulation Plus Ophthalmic Ointment Implementation* with Jessica Spires at Simulations Plus, Inc.
- New Contract (HHSF223201810182C) *A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drug*s with Narender Singh at CFD Research Corporation (CFDRC)
- New Grant (1U01FD006521) *Characterize Skin Physiology Parameters Utilized in Dermal Physiologically-Based Pharmacokinetic Model Development Across Different Skin Disease States* with Simcyp, Ltd.
- New Grant (1U01FD006514) *Computational Fluid Dynamics (CFD) and Discrete Element Modeling (DEM) Approach for Predictions of Dry Powder Inhaler (DPI) Drug Delivery* with Jari Tapani Kolehmainen at Princeton University
- New Grant (1U01FD006525) *Computational Fluid Dynamics (CFD) and Discrete Element Modeling (DEM) Approach for Predictions of Dry Powder Inhaler (DPI) Drug Delivery* with Kim Chan at University of Sydney
- New Grant (1U01FD006549) *Development of a Virtual Bioequivalence Trial Simulation Platform That Integrates Population Pharmacokinetic Modeling Algorithms into Physiologically-Based Pharmacokinetic Models* with Michael N. Neely at Children's Hospital of Los Angeles
- New Contract (HHSF223201810144C) *Evaluating Relationships Between In Vitro Nasal Spray Characterization Test Metrics for Bioequivalence and Nasal Deposition in Silico and In Vitro* with Laleh Golshahi at Virginia Commonwealth University

- New Grant (1U01FD006526) *Formulation Drug Product Quality Attributes in Dermal Physiologically-Based Pharmacokinetic Models for Topical Dermatological Drug Products and Transdermal Delivery Systems* with Jessica Spires at Simulations Plus, Inc.
- New Grant (1U01FD006522) *Formulation Drug Product Quality Attributes in Dermal Physiologically-Based Pharmacokinetic Models for Topical Dermatological Drug Products and Transdermal Delivery Systems* with Michael Roberts at University of Queensland
- New Contract (HHSF223201810188C) *Physiologically-Based Model of the Female Reproductive Tract: Vaginal and Intrauterine Delivery Components* with Robert R. Bies at University at Buffalo
- New Grant (1U01FD006537) *Three-Dimensional Approach for Modeling Nasal Mucociliary Clearance Via Computational Fluid Dynamics (CFD)* with Clement Kleinstreuer at North Carolina State University at Raleigh

Continuing Grants and Contracts

- Active Grant (1U01FD005232) *Physiologically Based Biopharmaceutics and Pharmacokinetics of Drug Products for Dermal Absorption in Humans* with Michael Roberts at University of South Australia
- Active Grant (1U01FD005225) *Development and Validation of Dermal PBPK Modeling Platform Toward Virtual Bioequivalence Assessment Considering Population Variability* with Sebastian Polak at Simcyp, Ltd.
- Active Grant (1U01FD005201) *Development of Hybrid CFD-PBPK Models for Absorption of Intranasal Corticosteroids* with Jeff Schroeter at Applied Research Associates, Inc.
- Active Grant (1U01FD005219) *An Integrated Multiscale-Multiphysics Modeling and Simulation of Ocular Drug Delivery with Whole-Body Pharmacokinetic Response* with Kay Sun at CFD Corporation
- Active Grant (1U01FD005211) *PBPK Modeling and Simulation for Ocular Dosage Forms* with Michael B Bolger at Simulations Plus
- Active Grant (1U01FD005206) *Physiologically Based Pharmacokinetic Model for Drugs Encapsulated into Liposomes* with Yanguang Cao at University of Buffalo
- Active Grant (1U01FD005214) *A Predictive Multiscale Computational Tool for Simulation of Lung Absorption and Pharmacokinetics and Optimization of Pulmonary Drug Delivery* with Narender Singh at CFD Corporation
- Active Grant (1U01FD005837) *A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways* with Ching-Long Lin at University of Iowa
- Active Grant (1U01FD005838) *Enhancing the Reliability, Efficiency, and Usability of Bayesian Population PBPK Modeling* with Brad Reisfeld at Colorado State University

Active Internal Research

- *Prediction of Tear Film Breakup Times for Ophthalmic Formulations CFD Models of Droplet Formulation From MDI*
- *Development of CFD-PBPK Models for Nasal Delivery of Abuse Deterrent Opioid Formulations*
- *CFD Analysis of Spreadability of Topical Formulations*
- *CFD Models of Soft Mist Inhalers*

Outcomes

Publications

- He, H., Liu, C., Wu, Y., Zhang, X., Fan, J., and Cao, Y. *A Multiscale Physiologically-Based Pharmacokinetic Model for Doxorubicin to Explore Its Mechanisms of Cytotoxicity and Cardiotoxicity in Human Physiological Contexts*. Pharm Res. (2018) **35**(9):174. doi: 10 . 1007/ s11095-018-2456-8. PMID: 29987398.
- Hsieh, N., Reisfeld, B., Bois, F., and WA., C. *Applying a Global Sensitivity Analysis Workflow to Improve the Computational Efficiencies in Physiologically-Based Pharmacokinetic Modeling*. Front Pharmacol. (2018) **9**:588. doi: 10.3389/fphar.2018.00588. PMID: 29937730.
- Kannan, R., Singh, N., and A., P. *A Compartment-Quasi-3d Multiscale Approach for Drug Absorption, Transport, and Retention in the Human Lungs*. Int J Numer Method Biomed Eng. (2018) **34**(5):e2955. doi: 10.1002/cnm.2955. PMID: 29272565.
- Kannan, R., Singh, N., and A., P. *A Quasi-3d Compartmental MultiScale Approach to Detect and Quantify Diseased Regional Lungconstriction Using Spirometry Data*. Int J Numer Method Biomed Eng. (2018) **34**(5):e2973. doi: 10.1002/cnm.2838. PMID: 29486525.
- Pak, J., Chen, Z. J., Sun, K., Przekwas, A., Walenga, R., and Fan, J. *Computational Modeling of Drug Transport Across the In Vitro Cornea*. Comput Biol Med. (2018) **92**:139–146. doi: 10.1016/j.compbiomed.2017.11.009. PMID: 29175100.
- Wittum, R., Naegel, A., Heisig, M., and Wittum, G. *Mathematical Modelling of the Viable Epidermis: Impact of the Cell Shape and Vetical Arrangement*. Mathematics and Mechanics of Solids. (2017): 1–14. doi:10.1177/1081286517743297.

Presentations

- Choi, J., LeBlanc, L. J., Choi, S., Haghighi, B., Hoffman, E. A., and Lin, C.-L. *Characteristcs of Inhaled Particle Deposition in the Lungs of Imaging-Based Asthma Clusters: A Numerical Study*. Presentation at ATS Preconference Current Practive and Future Development in Aerosol Medicine. San Diego, CA, May 19, 2018.
- Babiskin, A. *Physiologically-Based Absorption Modeling and Simulation Used in Assessing Bioequivalence for Ophthalmic Products*. Presentation at Complex Generic Drug Product Development Workshop. Silver Spring, MD, Sept. 12, 2018.
- Choi, J., LeBlanc, L. J., Choi, S., Haghighi, B., Hoffman, E. A., and Lin, C.-L. *Cluster-Guided Imaging-Based CFD Analysis of Airflow and Particle Deposition in Asthmatic Human Lungs*. Presentation at APS DFD. Denver, CO, Nov. 20, 2017.
- O'Shaughnessy, P., Altmaier, R., Walenga, R., and Lin, C.-L. *Verifying the Hygroscopic Particle Growth Model During the Time Relevant to Lung Inspiration*. Presentation at 10th International Aerosol Conference. St. Louis, MO, Sept. 3, 2018.
- Patel, N. *Skin in the Game: Mechanistic Modeling of Dermal Drug Absorption*. Presentation at The Certara Blog: PBPK Modeling & Simulation. Mar. 2, 2018.
- Singh, N., Kannan, R., and Przekwas, A. *A Multiscale Computational Framework for Inhalation Pharmacology and Drug Development*. Presentation at OINDP Workshop. Silver Spring, MD, Jan. 9, 2018.
- Tsakalozou, E. *Use of Modeling for Assessment of BE for Topical Products*. Presentation at Complex Generic Drug Product Development Workshop. Silver Spring, MD, Sept. 13, 2018.
- Walenga, R. *Computational Fluid Dynamics (CFD) Modeling for Product Development of Generic OINDPs and for Supporting Novel BE Approaches*. Presentation at Complex Generic Drug Product Development Workshop. Silver Spring, MD, Sept. 13, 2018.

Posters

- Abd, E., Mohammed, Y., Medley, G., Naegel, A., Grice, J., Maibach, H., and Roberts, M. *Relating Regional Variations in Skin Permeability to the Underlying Skin Morphology In Vivo*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Abdulla, T., Patel, N., Polak, S., Martins, F., Rostami-Hodjegan, A., and Jamei, M. *Quantitative Prediction of Dermal Drug Absorption Using MPML-Mechderma Model: Relative Effects of Application Site On Rivastigmine Pharmacokinetics From a Transdermal Delivery System*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Abdulla, T., Patel, N., Martins, F., Salem, F., Clarke, J., Jamei, M., and Polak, S. *Predicting the Pharmacokinetics of Topically Applied Ketoprofen Using Mechanistic Physiologically-Based Pharmacokinetics Modelling*. Poster Presentation at Perspective in Percutaneous Penetration. La Grande Motte, France, Apr. 4, 2018.
- Alinaghi, A., Cheruvu, H., Liu, X., Anissimov, Y., Kuswahyuning, R., Ghosh, P., Grice, J., Raney, S., and Roberts, M. *In Vitro-In Vivo Relationships (IVIVR) for Transdermal Delivery of Nicotine from Patches*. Poster Presentation at Perspective in Percutaneous Penetration. La Grande Motte, France, Apr. 4, 2018.
- Choi, J., LeBlanc, L., Choi, S., Haghighi, B., Hoffman, E., and Lin, C.L. *Cluster-Guided Imaging-Based CFD Analysis of Airflow and Particle Deposition in Asthmatic Human Lung*. Poster Presentation at American Physical Society. Denver, CO, Nov. 20, 2017.
- Choi, J., LeBlanc, L., Choi, S., Haghighi, B., Hoffman, E., O'Shaughnessy, P., Wenzel, S., Castro, M., Fain, S., Jarjour, N., Schiebler, M., Denlinger, L., and Lin, C.-L. *Characteristics of Inhaled Particle Deposition in the Lungs of Imaging-Based Asthma Clusters: A Numerical Study*. Poster Presentation at American Thoracic Society International Conference. San Diego, CA, May 21, 2018.
- Nan-Hung, H., Brad, R., Frederic, B., and Weihsueh, C. *Applying A Global Sensitivity Analysis Workflow to Improve Computational Efficiencies in Physiologically-Based Pharmacokinetic Model*. Poster Presentation at SOT Annual Meeting. San Antonio, TX, Mar. 11, 2018.
- LeMerdy, M., Eleftheria, T., Stephanie, C., Myong-Jin, K., Lin, X., Sharron, S., Ashok, C., Rodney, R., Murali, M., Liang, Z., Robert, L., and Jianghong, F. *Application of Ocular Physiologically Based Pharmacokinetic Modeling to Understand the Impact of Particle Size and Viscosity on Ophthalmic Bioavailability of Tobradex ST Suspension in Rabbits*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Martins, F., Patel, N., Salem, F., Jamei, M., and Polak, S. *Multi-Phase Multi-Layer Mechderma Model: Development, Verification and Application of a PBPK-PD Model of Dermal Absorption for Transdermal Product Assessment*. Poster Presentation at Perspective in Percutaneous Penetration. La Grande Motte, France, Apr. 4, 2018.
- Martins, F., Patel, N., Jamei, M., and Polak, S. *Mechanistic Physiologically Based Pharmacokinetic Modelling for Prediction of Dermal Absorption in Psoriatic Patients*. Poster Presentation at Perspective in Percutaneous Penetration. La Grande Motte, France, Apr. 4, 2018.
- Patel, N., Martins, F., Jamei, M., Ghosh, P., Raney, S., Zhang, X., Tsakalozou, E., Ni, Z., and Polak, S. *Integration of Physicochemical Product Characteristics Within a Mechanistic Dermal PBPK Model to Support Virtual Bioequivalence Evaluation of Topical Drug Products: A Case Study with Acyclovir Topical Creams*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Patel, N. and Polar, S. *Development of the Dermal Absorption Model for the Ketoprofen Local and Systemic Exposure Prediction*. Poster Presentation at Skin Forum 2018 Annual Meeting, June 20, 2018.

- Walenga, R., Babiskin, A., Absar, M., Zhang, X., Zhao, L., and Lionberger, R. *Modeling Approach for Assessing the Impact of Physicochemical Properties on Bioequivalence of Cyclosporine Ophthalmic Emulsion*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 14, 2017.