FY2018 GDUFA Science and Research Report: Locally-Acting Orally-Inhaled and Nasal Drug Products

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: Locally-Acting Orally-Inhaled and Nasal Drug Products (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm503040.htm)
- FY2016 GDUFA Science and Research Report: Locally-Acting Orally-Inhaled and Nasal Drug Products (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549167.htm
- FYs 2013-2017 GDUFA Science and Research Report: Locally-Acting Orally-Inhaled and Nasal Drug Products (https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm592245.htm)

Introduction

Performance of orally inhaled and nasal drug products (OINDPs) is governed by complex interactions between device, formulation, and patient factors. Because existing in vitro methods have limited predictability of these interactions, both development and bioequivalence (BE) demonstration of generic OINDPs is very challenging, time-consuming, and expensive, in part due to their reliance on in vivo studies. For this reason, even though there is a current, clear regulatory pathway utilizing the weight-of-evidence approach for BE assessment of OINDPs, FDA continues to explore new methods to make development and BE assessment of OINDPs more cost-efficient and time-effective. These research initiatives can be broadly separated into four categories:

1) Identification of formulation and device variables which are important for successful development of generic OINDPs;

2) Development of clinically relevant in vitro tools for the prediction of in vivo regional drug deposition and dissolution from OINDPs;

3) Development of computational fluid dynamic (CFD) and physiologically-based pharmacokinetic (PBPK) models for the prediction of the fate of drugs delivered through OINDPs and to assess their applicability in generic OINDP development programs; and,

4) Identification, validation, and standardization of novel techniques that may have the potential to reduce the burden of current BE requirements for generic OINDPs.

Under these initiatives, FDA has explored advanced in vitro/in silico methods such as CFD modeling and clinically relevant in vitro dissolution and deposition tests to understand and predict performance of OINDPs in a more realistic way. These clinically relevant in vitro methods have shown good in vivo predictability of regional nasal and lung drug deposition and dissolution, as well as local and systemic drug bioavailability of OINDPs. Some of these methods are described below.

Research

To date, three different extramural projects have considered in vitro dissolution techniques, with discriminatory and reproducible in vitro dissolution results, across a range of inhaled corticosteroid products, with the goal of developing a methodology to be utilized as a standardized dissolution method for compendial release testing, or for bioequivalence assessment of generic OINDPs. Together, these three dissolution grants are providing FDA with methods by which we can measure parameters in vitro to provide a correlation to the in vivo effects of these OIDPs. When a reliable, robust method of dissolution can be clearly described in the literature and reproduced in various labs, and potentially combined with CFD modeling methodologies, drug applicants can utilize those methods as a means of supporting their generic drug development programs. Further, applicants may potentially be able to forego a costly comparative clinical endpoint BE study, which may be less sensitive to formulation differences.

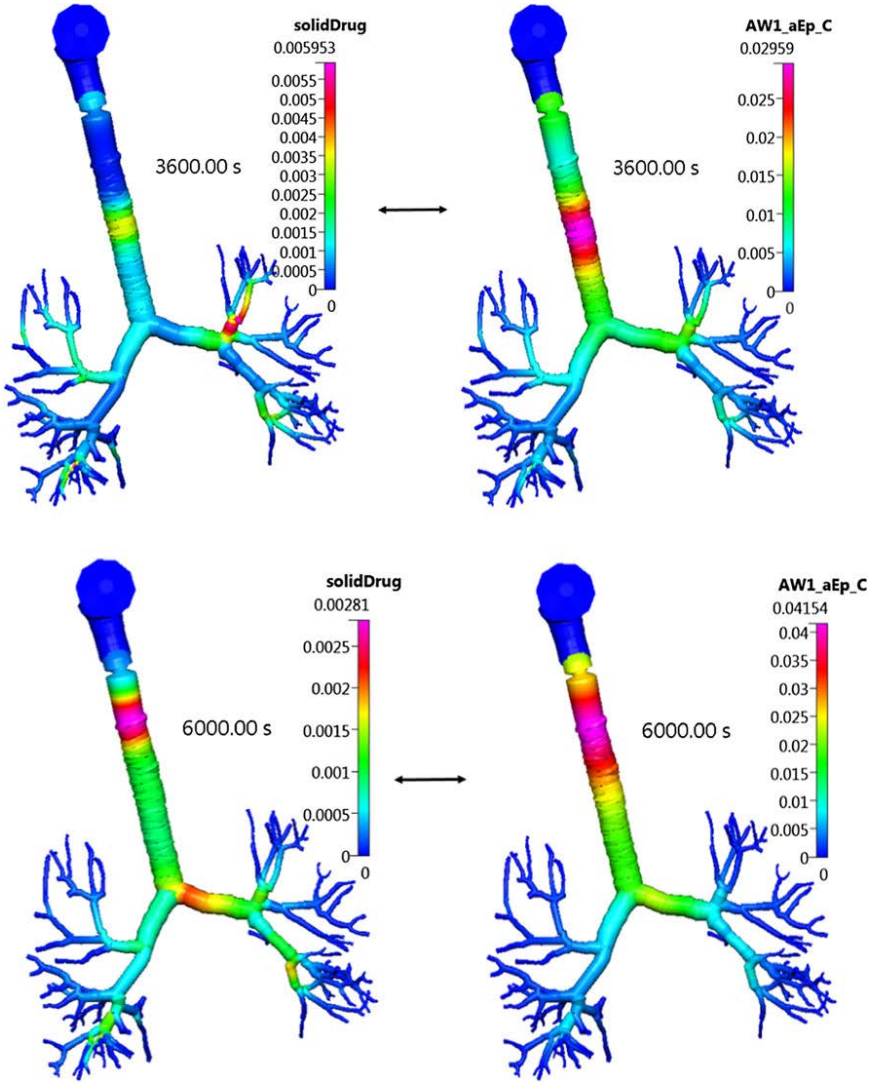
Another research initiative-based program utilized CFD and PBPK models, which were developed to predict deposition, tissue concentration, blood concentration, and pharmacodynamic (PD) outcome after administration of locally acting OINDPs. This project created a 3-dimensional model of the oropharynx to the eighth generation of airways and predicted drug transit and deposition [see **Figure 1**]. CFD and PBPK models were also developed to predict deposition, tissue concentration, and blood concentration after intranasal administration of a corticosteroid nasal spray. The model took into consideration multiple drug products and numerous device use variables. Results indicated that regional deposition from nasal sprays is most sensitive to disease state (healthy vs. rhinitic), insertion depth, and nozzle positioning. Actuation force, cone angle, and air flow rate did not show large effects on regional deposition. The PBPK model was able to match in vivo experimental results well in some cases.

Additional research is ongoing to explore physicochemical API properties and device characteristics to demonstrate structural similarities (Q3) between test and reference Dry Powder Inhaler (DPI), Metered Dose Inhaler (MDI), and nasal products. A series of projects are exploring these Q3 characteristics, using Morphologically Directed Raman Spectroscopy (MDRS) in conjunction with in vitro dissolution, more realistic Aerodynamic Particle Size Distribution (APSD) measurement under realistic in vitro testing conditions, and particle surface characterization [see **Figure 2**]. The goal of this initiative is to provide greater understanding of the complex interactions between device, formulation, and patient factors, and eventually be able to predict the therapeutic behavior based on these in vitro characteristics.

FDA laboratories have developed several research projects to evaluate the product quality and performance of nasal spray and DPIs in support of ANDA reviews. FDA laboratories are currently working on a research project to evaluate the Spiriva Handihaler.

In recent years, the FDA has approved many NDAs using new inhalation devices and novel delivery approaches [see **Figure 3**]. Thus, for future generic applications, a thorough understanding of these next generation inhalation drug delivery systems is necessary. FDA is actively working to develop in vitro particle sizing methods for evaluating the new devices. Current projects include laser diffraction studies on soft mist inhalers and breath-actuated nasal spray delivery systems.

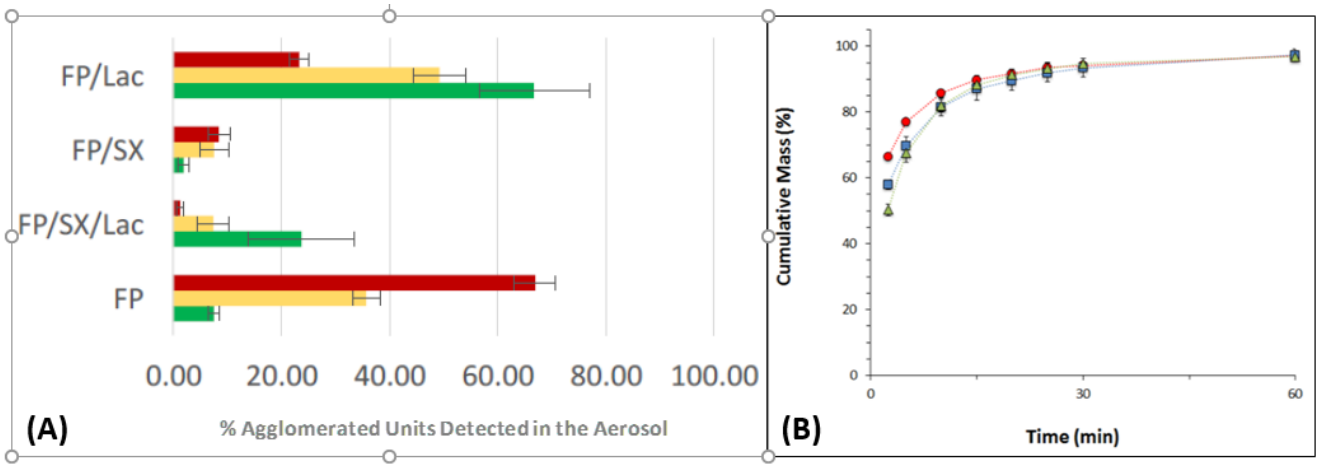
Figure 1. Local Drug Concentration Predictions of Solid and Dissolved Fluticasone Propionate in the Lung Surface Lining Liquid Layer in the Quasi-3D Model at Different Times (Courtesy of Kannan et al., 2018).[1]



Solid and dissolved fluticasone propionate concentration predictions (kg/m^3) in the quasi-3D model after drug mass of 1000 µg is inhaled. The top panel (A) shows solid drug (left) and dissolved drug (right) at 3600 s, while the bottom panel (B) shows solid drug (left) and dissolved drug (right) at 6000 s.

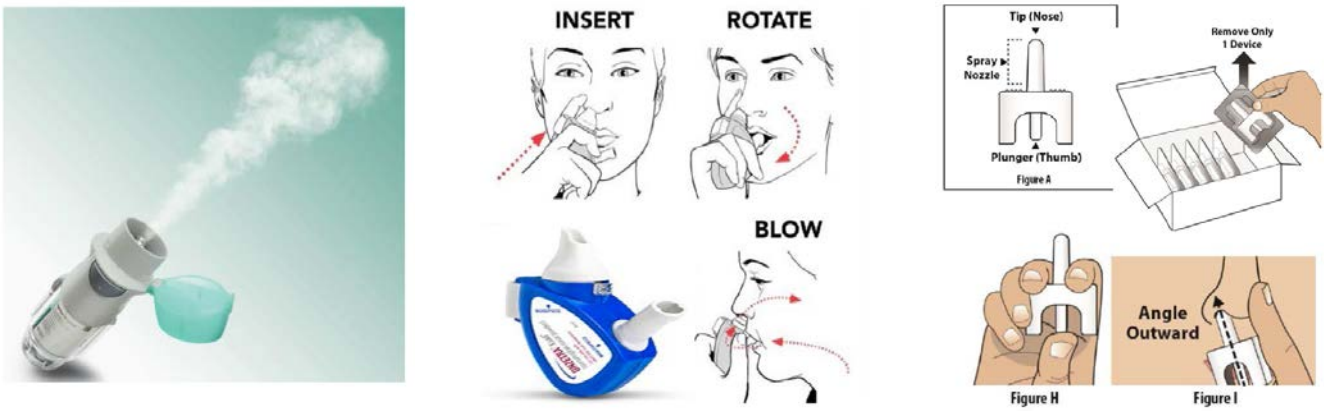
[1] Kannan, R., Singh, N., and A., P. *A Compartment-Quasi-3d Multiscale Approach for Drug Absorption, Transport, and Retention in the Human Lungs*. Int J Numer Method Biomed Eng. (2018) **34**(5):e2955. doi: 10.1002/cnm.2955. PMID: 29272565.

Figure 2. MDRS (A) and In-Vitro Dissolution (B) Data of the Aerosols of Advair® Diskus® at Different Strengths.



(A) MDRS data of impactor-sized mass (ISM) collected from the three strengths of Advair® Diskus® [100/50 µg (green), 250/50 µg (yellow) and 500/50 µg (red) fluticasone propionate/salmeterol]. **(B)** Dissolution rate of fluticasone propionate in the ISM collected from the three strengths of Advair® Diskus® [100/50 µg (red), 250/50 µg (blue) and 500/50 µg (green) fluticasone propionate/salmeterol].

Figure 3. Examples of Novel Inhalation Devices Under Internal FDA Research. From left to right: Spiriva Respimat Soft Mist Inhaler, Onzetra Xsail Nasal Spray Powder, Imitrex Nasal Spray



Research Projects and Collaborations

New Grants and Contracts

- New Contract (HHSF223201810182C) *A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drugs* with Narender Singh PhD at CFD Research Corporation (CFDRC)
- New Grant (1U01FD006514) *Computational Fluid Dynamics (CFD) and Discrete Element Modeling (DEM) Approach for Predictions of Dry Powder Inhaler (DPI) Drug Delivery* with 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 University of Sydney
- New Contract (HHSF223201810169C) *Evaluating Batch to Batch Variability and Its Origins in Dry Powder Inhalers* with Hugh D C Smyth at The University of Texas at Austin, College of Pharmacy
- 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 (1U01FD006537) *Three-Dimensional Approach for Modeling Nasal Mucociliary Clearance Via Computational Fluid Dynamics (CFD)* with North Carolina State University Raleigh

Continuing Grants and Contracts

- Active Contract (HHSF223201610099C) *Pharmacokinetic Comparison of Locally Acting Inhaled Drug Products* with Jurgen Bulitta at University of Florida
- Active Grant (1U01FD004941*) In Vitro Fluid Capacity-Limited Dissolution Testing and Its Kinetic Relation to In Vivo Clinical Pharmacokinetics for Orally Inhaled Drug Products* with Masahiro Sakagami at Virginia Commonwealth University
- Active Contract (HHSF223201310220C) *Investigate the Sensitivity of Pharmacokinetics in Detecting Differences in Physicochemical Properties of the Active in Suspension Nasal Products for Local Action* with Guenther Hochhaus at University of Florida
- Active Grant (1U01FD005201) *Development of Hybrid CFD-PBPK Models for Absorption of Intranasal Corticosteroids* with Jeff Schroeter at Applied Research Associates, Inc.
- 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 (5U01FD004943) *Comprehensive Evaluation of Formulation Effects on Metered Dose Inhaler Performance* with Guenther Hochhaus at University of Florida
  Active Grant (1U01FD005837) *A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways* with Ching-Long Lin at University of Iowa
- Active Contract (HHSF223201710163C) *Investigating Orthogonal Analytical Approaches to Demonstrate Bioequivalence of Nasal Suspension Formulations* with Robert Price at University of Bath
- Active Contract (HHSF223201710116C) *Investigating the Microstructure of Dry Powder Inhalers Using Orthogonal Analytical Approaches* with Robert Price (PI) and Jag Shur (CI) at University of Bath
- Active Contract (HHSF223201710072C) *Patient's Perception of Dry Powder Inhaler Airflow Resistance* with Omar Usmani at Imperial College of Science and Technology, London

Active FDA Research

- *Particle Size Characterization in Nasal Spray Suspensions Using MDRS Method*
- *Suitability Evaluation of Abbreviated Impactor Measurement (AIM) Method for Characterization of Orally Inhaled Products (OIPs)*
- *Physiological Mouth-Throat Models for Inhalation Products*
- *In Vitro Performance Testing of Soft Mist Inhalers*
- *Product Quality and Performance Evaluation of Spiriva Handihaler*
- *Particle Size Distribution (PSD) by Laser Diffraction for Onzetra Xsail Nasal Spray Powder*

- *Chi Square Ratio Analysis of Aerodynamic Particle Size Distribution (APSD) by Multiple-Stage Cascade Impactor CFD Models of Droplet Formulation From MDI*
- *CFD Models of Soft Mist Inhalers*
- *Batch to Batch Variability of Inhalation Products*

Outcomes

Product Specific Guidances

- *New Draft Guidance for Azelastine Hydrochloride Nasal Spray, Metered*. FDA Guidance Posting. Oct. 19, 2017. Link to Posting.
- *New Draft Guidance for Fluticasone Propionate Inhalation Aerosol, Metered*. FDA Guidance Posting. Oct. 19, 2017. Link to Posting.
- *New Draft Guidance for Fluticasone Propionate Inhalation Powder*. FDA Guidance Posting. Oct. 19, 2017. Link to Posting.
- *New Draft Guidance for Mometasone Furoate Inhalation Powder*. FDA Guidance Posting. Oct. 19, 2017. Link to Posting.
- *New Draft Guidance for Salmeterol Xinafoate Inhalation Powder*. FDA Guidance Posting. Oct. 19, 2017. Link to Posting.
- *New Draft Guidance for Tiotropium Bromide Inhalation Powder*. FDA Guidance Posting. Oct. 19, 2017. Link to Posting.
- *Revised Draft Guidance for Ketorolac Tromethamine Nasal Spray, Metered*. FDA Guidance Posting. Feb. 8, 2018. Link to Posting.
- *New Draft Guidance for Beclomethasone Dipropionate Nasal Aerosol, Metered*. FDA Guidance Posting. July 20, 2018. Link to Posting.
- *Revised Draft Guidance for Fluticasone Propionate Inhalation Aerosol, Metered*. FDA Guidance Posting. July 20, 2018. Link to Posting.
- *New Draft Guidance for Albuterol Sulfate Inhalation Powder, Metered*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.
- *New Draft Guidance for Talc Intrapleural Aerosol, Metered*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.

Publications

- Choi, S. H., Wang, Y., Conti, D. S., Raney, S. G., Delvadia, R., Leboeuf,A., and Witzmann, K. *Generic Drug Device Combination Products: Regulatory and Scientific Considerations*. Int J Pharm. (2018) **544**(2):443–454. doi: 10 . 1016 / j . ijpharm . 2017 . 11 . 038. PMID: 29170118.
- 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 Multi Scale Approach to Detect and Quantify Diseased Regional Lung Constriction Using Spirometry Data*. Int J Numer Method Biomed Eng. (2018) **34**(5):e2973. doi: 10.1002/cnm.2838. PMID: 29486525.
- Lionberger, R. *New Tools for Generic Orally Inhaled Drug Products to Maximize Prospects of Food and Drug Administration Approval*. Respiratory Drug Delivery. (2018) **1**:221–230.
- Price, R., Farias, G., Ganley, W., and Shur, J. *Demonstrating Q3 Structural Equivalence of Dry Powder Inhaler Blends: New Analytical Concepts and Techniques*. Respiratory Drug Delivery. (2018) **1**:265–276.
- Schroeter, J. D., Sheth, P., Hickey, A. J., Asgharian, B., Price, O. T., Holt, J. T., Conti, D. S., and Saluja,

B. *Effects of Formulation Variables on Lung Dosimetry of Albuterol Sulfate Suspension and Beclomethasone Dipropionate Solution Metered Dose Inhalers*. AAPS PharmSciTech. (2018) **19**(5):2335–2345. doi: 10.1208/s12249-018 1071-7. PMID: 29858973.

- Wei, X., Hindle, M., Kaviratna, A., Huynh, B. K., Delvadia, R. R., Sandell, D., and Byron, P. R. *In Vitro Tests for Aerosol Deposition. VI: Realistic Testing with Different Mouth-Throat Models and In VitroIn Vivo Correlations for a Dry Powder Inhaler, Metered Dose Inhaler, and Soft Mist Inhaler*. J Aerosol Med Pulm Drug Deliv. (2018): 1. doi:10.1089/jamp.2018.1454. PMID: 29878859.
- Witzmann, K. A. *The Role of Comparative Analyses for Evaluation of Generic Drug-Device Combinations in an Abbreviated New Drug Application*. Respiratory Drug Delivery. (2018) **1**:231–236.

Presentations

- Choi, J., LeBlanc, L. J., Choi, S., Haghighi, B., Hoffman, E. A., and Lin, C.-L. *Characteristics of Inhaled Particle Deposition in the Lungs of Imaging-Based Asthma Clusters: A Numerical Study*. Presentation at ATS Preconference Current Practice and Future Development in Aerosol Medicine. San Diego, CA, May 19, 2018.
- Byron, P. *Clinically Relevant In Vitro Testing of Oral Inhalation Products Using Realistic Mouth-Throat Models*. Presentation at OINDP Workshop. Silver Spring, MD, Jan. 9, 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.
- Conti, D. *Emerging Technologies for Bioequivalence of Generic Complex Drug-Device Combination Products*. Presentation at IFPAC. North Bethesda, MD, Feb. 14, 2018.
- Conti, D. *Current Product-Specific Guidances and Common Questions in Pre-ANDA Communications*. Presentation at Complex Generic Drug Product Development Workshop. Silver Spring, MD, Sept. 13, 2018.
- Guo, C. *Analytical Method Development for Ingredient-Specific Particle Sizing of Nasal Spray Suspensions*. Presentation at OINDP Workshop. Silver Spring, MD, Jan. 9, 2018.
- Hindle, M. *Comparing Nasal Suspension Products Using Realistic In Vitro Test Methods*. Presentation at OINDP Workshop. Silver Spring, MD, Jan. 9, 2018.
- Hochhaus, G. *Development of an Optimized Dissolution Test System for Oindps*. Presentation at OINDP Workshop. Silver Spring, MD, Jan. 9, 2018.
- Jiang, X. *Session 2: Novel Analytical Tools for Characterization of Nasal Suspensions*. Presentation at OINDP Workshop. Silver Spring, MD, Jan. 9, 2018.
- Li, M. *Batch-to-Batch Pharmacokinetic Variability of Orally Inhaled Drug Products*. Presentation at Complex Generic Drug Product Development Workshop. Silver Spring, MD, Sept. 13, 2018.
- Lionberger, R. *New Tools for Generic OINDPS to Maximize Prospects of FDA Approval*. Presentation at RDD 2018. Tuscon, AZ, Apr. 22, 2018.
- Luke, M. *Session 3: Realistic Models for Prediction of Regional Drug Deposition from Orally Inhaled and Nasal Drug Products (Oindps)*. Presentation at OINDP Workshop. Silver Spring, MD, Jan. 9, 2018.
- 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.
- Price, R. *Dissolution and Beyond: The Use of Advanced Structural Characterization Tool for Demonstrating Pharmaceutical Equivalence of Orally Inhaled Drug Products*. Presentation at OINDP Workshop. Silver Spring, MD, Jan. 9, 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.
- Rodriguez, J. *Development of Enhanced Analytical Tools for Evaluation of Complex Generic Products*. Presentation at IFPAC. Bethesda, MD, Feb. 14, 2018.
- Rodriguez, J. *Enhanced Analytical Tools for Bioequivalence Evaluation of Nasal Spray Drug Products*. Presentation at DIA Combination Products. Silver Spring, MD, Oct. 9, 2018.
- Sakagami, M. *Discriminative In Vitro Dissolution Testing for Orally Inhaled Drug Products*. Presentation at OINDP Workshop. Silver Spring, MD, Jan. 9, 2018.
- Schroeter, J. *A CFD-PBPK Approach to Simulate Deposition, Absorption, and Bioavailability of Intranasal Corticosteroids*. Presentation at OINDP Workshop. Silver Spring, MD, Jan. 9, 2018.
- Shur, J. *Advanced Characterization Approaches to Demonstrate Bioequivalence of Nasal Suspension Drug Products*. Presentation at OINDP Workshop. Silver Spring, MD, Jan. 9, 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.
- Witzmann, K. *Overcoming Barriers to Entry for Complex Generic Oral Inhalation Drug Products*. Presentation at DIA Webinar. Silver Spring, MD, Mar. 15, 2018.
- Witzmann, K. *The Role of Comparative Analyses for Evaluation of Generic Drug-Device Combinations in an ANDA*. Presentation at RDD 2018. Tuscon, AZ, Apr. 26, 2018.
- Witzmann, K. *Generic Drug Development for Respiratory Products, US Food and Drug Administration Update*. Presentation at ATS 2018. San Diego, CA, May 23, 2018.
- Witzmann, K. *Overview of Regulatory and User-Interface Considerations, and the Role of Comparative Analyses, in Developing a Generic Drug-Device Combination Product in an ANDA*. Presentation at Complex Generic Drug Product Development Workshop. Silver Spring, MD, Sept. 12, 2018.
- Zhang, L. *Opening Remarks*. Presentation at OINDP Workshop. Silver Spring, MD, Jan. 9, 2018.
- Zhao, L. *Session 4: Computational Models to Understand In Vivo Performance of OINDPs*. Presentation at OINDP Workshop. Silver Spring, MD, Jan. 9, 2018.

Posters

- 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.
- Kaviratna, A., Ngo, D., Liu, X., Delvadia, R., and Guo, C. *Evaluation of Bio-Relevant Mouth-Throat (MT) Models to Determine the Aerosol Deposition and Particle Size Distribution of a Dry Powder inhaler (DPI)*. Poster Presentation at AAPS 2017 Annual Meeting, San Diego, CA, Nov. 12, 2017.
- Kurumaddali, A., Schilling, U., Chen, M., Jiao, Y., Seay, Y., Baumstein, S., Abu-Hasan, M., Conti, D., Oguntimein, M., Delvadia, R., Winner, L., Tabulov, C., Saluja, B., Bulitta, J., and Hochhaus, G. *Inhalation Profile Modeling for Fluticasone Propionate Dry Powder Inhalers in Healthy Volunteers During A Four Way Crossover Bioequivalence Study*. Poster Presentation at ASCPT Annual Meeting. Orlando, FL, Mar. 21, 2018.
- Wood, E. and Tyner, K. *A Critical Evaluation of Emerging High Resolution Imaging Technologies for*

the Characterization of Complex Formulations. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.