FY2018 GDUFA Science and Research Report: Ophthalmic 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: Ophthalmic Products (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm508095.htm)
- FY2016 GDUFA Science and Research Report: Ophthalmic Products (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549164.htm)
- FYs 2013-2017 GDUFA Science and Research Report: Ophthalmic Products (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm597035.htm)

Introduction

Significant progress has been made in FDA's ongoing research to better understand how ophthalmic products work at their site of action and translate this understanding into new methods to establish bioequivalence. As part of the FY2018 GDUFA Research Priorities, 3 new contracts were awarded. In addition, 2 grants and 1 contract were active in FY18 as well as eight internal research projects. The research aims of these research projects are to:

- Develop physicochemical characterization methods to assess and compare formulation critical quality attributes
- Investigate key physicochemical properties that affect drug release and ocular bioavailability
- Develop in vitro release testing methods which are sensitive to formulation difference and/or predictive of in vivo release
- Develop and better understand in vitro-in vivo correlations
- Predictive modeling of ocular drug absorption that can assess impact of Q3 formulation changes

Research

To investigate new and sensitive methods for assessing complex topical formulations, FDA awarded contract HHSF223201610105C to Physical Pharmaceutica, LLC on September 16, 2016. This contract, which ended on January 15, 2018, developed a pulsatile microanalysis (PMD) method to study drug release from cyclosporine emulsion formulations. Using PMD, cyclosporine drug release can be measured as early as 40 seconds from the start of the study, and the method was demonstrated to be sensitive to changes in drug concentration, temperature, and manufacturing process. In addition, it illustrated that PMD is a method for evaluating drug release at early time points, which may be particularly relevant for drugs with short residence times. These findings have helped provide a better understanding of how the manufacturing process and local environment can affect drug distribution in the formulation as well as describe potential mechanisms of drug release from the different components within the formulation.

Grant #1U01FD005211 was awarded to Dr. Michael Bolger (Simulations Plus, Inc.) in September 2014 to develop the Ocular Compartmental Absorption and Transit (OCAT™) model in GastroPlus™ for ophthalmic suspension formulation. This OCAT model is now being tested internally to study the impact of formulation physicochemical properties on ocular drug in vivo PK performance. Dexamethasone ophthalmic suspensions were used as the initial model drug. To obtain adequate data for model verification, an internal study was also conducted to

measure dexamethasone distribution in ocular tissues and plasma in rabbits following ocular administration of a tobramycin/dexamethasone suspension.

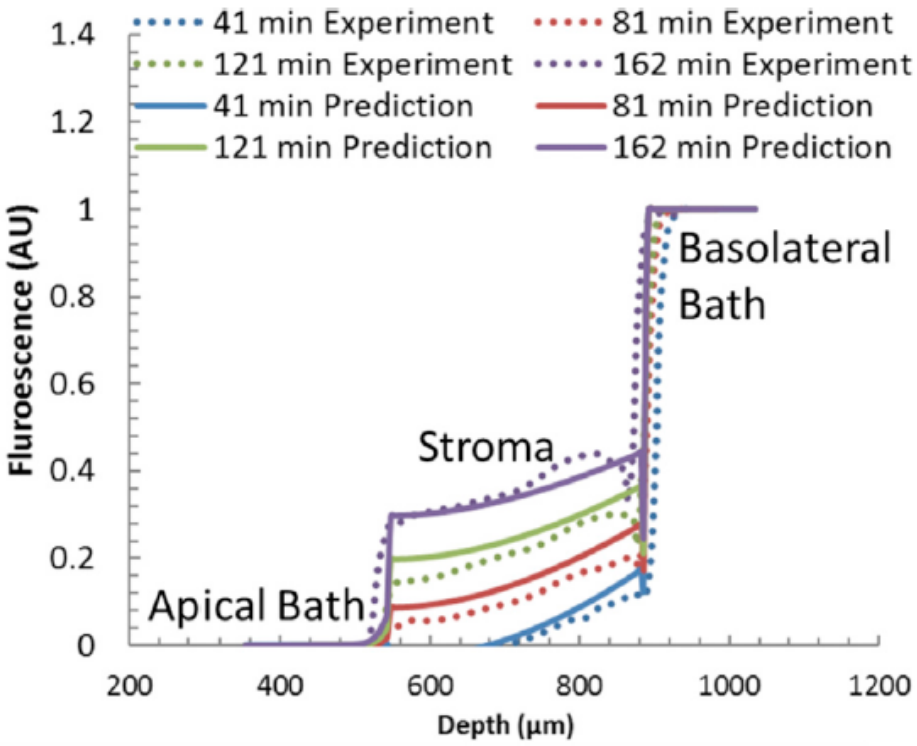
Grant #1U01FD005219 was awarded to Kay Sun (CFD Research Corporation) to develop a multiscale model for ocular delivery, absorption, and distribution of ophthalmic drug products using CFD's computational biology (CoBi) tools coupled to PBPK approach in human, animal models, and in vitro rabbit ocular barriers (**Figure 1**). This model would simulate ocular drug delivery and its interaction locally and systemically within the whole body, thereby providing an accurate and efficient computational platform for ocular drug products. Part of the finding has been published recently in *Computers in Biology and Medicine 2018, 92:139-146*.

To ensure the approval of high quality generics, an internal collaboration evaluated dose content uniformity concentration testing of multi-dose suspension products to ensure that these products dispense a controlled and accurate amount of drug throughout the product's intended usage (e.g., beginning, middle, and end use of the multi-dose bottle). The results shown in **Figure 2** illustrate that such testing can clearly differentiate between products that have differences in resuspendability and short-term particle stability that can affect product quality and patient dosing amounts.

Measurement of particle size distribution (PSD) of non-solution ophthalmic products exhibiting complex rheological behaviors (e.g., emulsions, suspensions, ointments) can be challenging. Therefore, several internal projects focused on identifying the appropriate technique(s) or method(s) to allow reliable measurements of the PSD. For example, an in-depth assessment of cyclosporine emulsion PSD was performed using five different particle sizing techniques and found that the variability of reported particle size increased, and was not as accurate, for emulsions dispersed in a non-Newtonian fluid and at higher emulsion concentrations (Petrochenko et al, Int J Pharm, 2018). Furthermore, advanced separation techniques including asymmetric flow field flow fractionation were found to be useful and provided valuable insight into the effect of polydispersity of the size measurement of emulsions (Qu et al, Int J Pharm, 2018). FDA laboratories also evaluated the impact of manufacturing processes on the critical quality attributes (e.g., PSD, rheological properties, etc.) of the ophthalmic drug products to ensure that critical process parameters could be approproiately identified and controlled (Dong et al, Int J Pharm, 2018). Novel techniques, such as tip-enhanced Raman spectroscopy, and darkfield microscopy with hyperspectral imaging are also being explored to expand analytical capabilities.

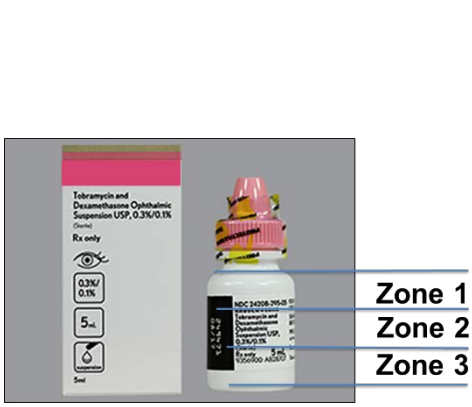
Another internal project developed a unique biphasic diffusion method to evaluate the effect of formulation and environmental related variables on emulsion drug distribution and release. The setup (**Figure 3**) enabled the determination of the rate and extent of drug distribution, under both static (e.g., during storage) and dynamic conditions (e.g., during in vitro drug release testing or after in vivo administration). This work has improved the general understanding of the process of drug distribution and mechanism of drug release in emulsion dosage form.

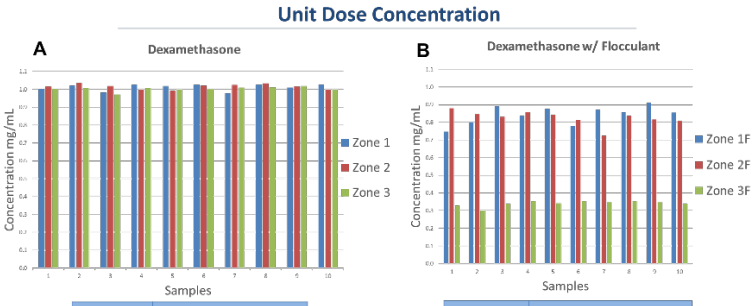
Figure 1. Spatial Fluorescence and CoBi Q3D Model Prediction of Fluorescein Across Rabbit Cornea.



The corneal endothelium is around the 870 µm mark while the epithelium is near 550 µm. Tissue fluorescence displayed as arbitrary units (AU).[1]

Figure 2. Unit Dose Analysis Testing of Topical Ophthalmic Suspension Products.





Zone 1	1.012 ± 0.018 mg/mL
Zone 2	1.015 ± 0.015 mg/mL
Zone 3	1.002 ± 0.013 mg/mL

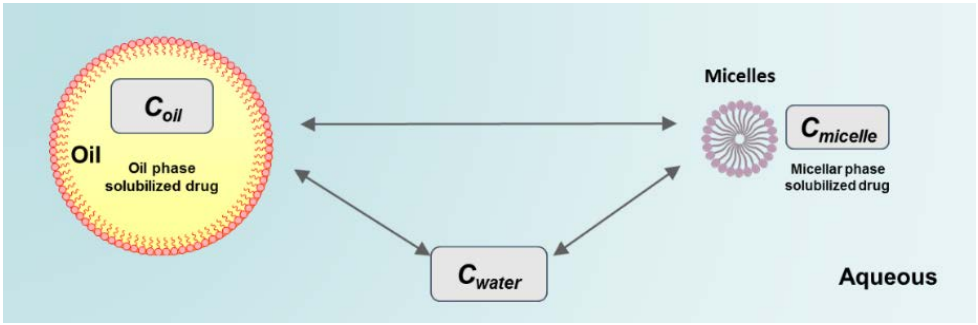
Zone 1F	0.842 ± 0.051 mg/mL
Zone 2F	0.825 ± 0.040 mg/mL
Zone 3F	0.314 ± 0.017 mg/mL

[1] Pak J, Chen ZJ, Sun K, Przekwas A, Walenga R, Fan J. *Computational Modeling of Drug Transport Across the In Vitro Cornea.* Computers in biology and medicine. 2018; 92:139-146.

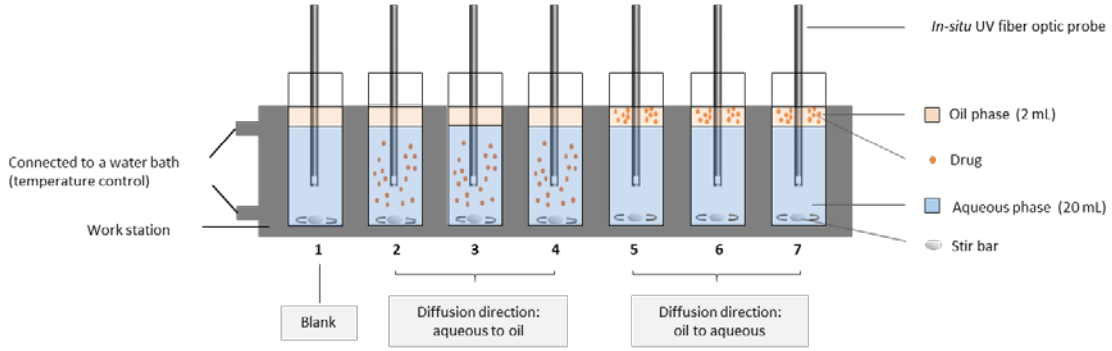
The unit dose concentration of ophthalmic suspension sampled from the beginning, middle and the end of the bottle (zone 1 to zone 3). The unit dose concentration of dexamethasone in the original bottle is consistent to the labeled strength in all the three zones, while the unit dose concentration decreases from the zone 1 to zone 3 in the flocculated product.

Figure 3. A Biphasic Diffusion Method to Understand Drug Distribution and Release in Emulsions.

A



B



The phase composition and complex drug diffusion in the microenvironment of an emulsion formulation (A) and the biphasic diffusion experimental setup (B) for evaluating the effects of formulation, and environment related variables.

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 Implemenation* with Jessica Spires at Simulations Plus, Inc.
- New Contract (HHSF223201810114C) *In Vitro and In Vivo Assessment of Ophthalmic Ointments for Generic Product Equivalence* with Xiuling Lu at University of Connecticut

Continuing Grants and Contracts

- 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 Contract (HHSF223201610105C) *Pulsatile Microdialysis for In Vitro Release of Ophthalmic Emulsions* with Robert Bellantone at Physical Pharmaceutica LLC

Active FDA Research

- *Physicochemical Characterization of Topical Ophthalmic Emulsion Products*
- *Physicochemical Characterization of Topical Ophthalmic Suspension Products*
- *In Vivo Biodistribution Evaluation of Opthalmic Suspension Drug Products*
- *New Method and Analytical Technique for Characterization and Performance Evaluation of Ophthalmic Formulations*
- *Assessing the Impact of Manufacturing Process on the Physicochemical Properties and Performance Attributes of Ophthalmic Formulations*
- *Development of the Earth Movers Distance for Particle Size Distribution Comparisons*
- *Prediction of Tear Film Breakup Times for Ophthalmic Formulations*
- *Assessing and Predicting Ocular Bioavailability with Changes in Critical Formulation Ingredients (Preservatives) and Properties*

Outcomes

Product-Specific Guidances

- *New Draft Guidance for Ciprofloxacin Hydrochloride Ophthalmic Ointment*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.
- *New Draft Guidance for Dexamethasone;Neomycin Sulfate;Polymyxin B Sulfate Ophthalmic Suspension, Drops.* FDA Guidance Posting. July 20, 2018. Link to Posting.
- *New Draft Guidance for Fluorometholone Ophthalmic Suspension, Drops*. FDA Guidance Posting. Oct. 19, 2017. Link to Posting.
- *New Draft Guidance for Loteprednol Etabonate Ophthalmic Ointment*. Link to Posting
- *New Draft Guidance for Loteprednol Etabonate Ophthalmic Suspension, Drops*. FDA Guidance Posting. Feb. 8, 2018. Link to Posting.
- *New Draft Guidance for Triamcinolone Acetonide Intravitreal Injectable*. Link to Posting
- *Revised Draft Guidance for Loteprednol Etabonate Ophthalmic Suspension, Drops*. FDA Guidance Posting. Feb. 8, 2018. Link to Posting.

Publications

- Bao, Q., Newman, B., Wang, Y., Choi, S., and Burgess, D. *In Vitro and Ex Vivo Correlation of Drug Release from Ophthalmic Ointments*. Journal of Controlled Release. (2018) **276**:93–101. doi: 10.1016/j. ijpharm.2017.04.075. PMID: 29518465.
- Dong, Y., Qu, H., Pavurala, N., Wang J., Sekar V., Martinez, M., Fahmy, R., Ashraf, M., Cruz, C.N., and Xu, X. *Effect of Formulation and Process Variables on the Properties of Cyclosporine Ophthalmic Ointments*. International Journal of Pharmaceutics. (2018), 544(1): 254-264. doi: 10.1016/j.ijpharm.2018.04.042. PMID: 29684560.
- Hu, M., Jiang, X., Absar, M., Choi, S., Kozak, D., Shen, M., Weng, Y., Zhao, L., and Lionberger, R.

Equivalence Testing of Complex Particle Size Distribution Profiles Based on Earth Mover's Distance. AAPS J. (2018) **20**(3):62. doi: 10.1208/s12248-018-0212-y. PMID:29651627.

- Matta, M., Narayanasamy, S., Thomas, C., Xu, L., Stewart, S., Chockalingam, A., Patel, V., and Rouse, R. *A Sensitive UPLC-APCI-MS/MS Method for the Determination of Dexamethasone and Its Application in an Ocular Tissue Distribution Study in Rabbits Following Topical Administration*. Anal.Methods. (2018) **10**:2307–2316. doi: 10.1039/ C8AY00283E.
- 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.
- Patere, S., Newman, B., Wang, Y., Choi, S., Vora, S., Ma, A., Jay, M., and Lu, X. *Infl e of Manufacturing Process Variables On the Properties of Ophthalmic Ointments of Tobramycin*. Pharm Res. (2018) **35**(9):179. doi: 10.1016/j.compbiomed. 2017.11.009. PMID: 30046909.
- Patil, S. M., Li, V., Peng, J., Kozak D., Xu, J., Cai, B., Keire, D. A. & Chen, K. *A Simple and Non-invasive DOSY NMR Method for Droplet Size Measurement of Intact Oil-in-Water Emulsion Drug Products*. J. Pharm. Sci. (2018) **108**(2): 815-820. doi: 10.1016/j.xphs.2018.09.027. PMID: 30291851.
- Petrochenko, P., Pavurala, N., Wu, Y., Wong, S.Y. Parhiz, H., Chen, K., Patil, S., Qu, H., Buoniconti, P., Mohammad, A., Choi, S., Ashraf, M., Cruz, C.N., Zheng, J., Xu, X. *Analytical Considerations for Measuring the Globule Size Distribution of Cyclosporine Ophthalmic Emulsions*. International Journal of Pharmaceutics (2018) **550**(1-2):229-239. doi: 10.1016/j.ijpharm.2018.08.030. PMID: 30125649.
- Qu, H., Wang, J., Wu, Y., Zheng, J., Krishnaiah, Y. S. R., Absar, M., Choi, S., Ashraf, M., Cruz, C. N., and Xu, X. *Asymmetric Flow Field Flow Fractionation for the Characterization of Globule Size Distribution in Complex Formulations: A Cyclosporine Ophthalmic Emulsion Case*. Int J Pharm. (2018) **538**(1-2):215–222. doi: 10.1016/j. ijpharm.2018.01.012. PMID: 29341918.
- Wang, J., Kumeria, T., Bezem, M., Wang, J., and Sailor, M. *Self- Reporting Photoluminescent Porous Silicon Microparticles for Drug De- livery*. ACS Appl. Mater. Interfaces. (2018) **10**(4):3200–3209. doi: 10.1021/acsami.7b09071.
- Wang, X., Patil, S.M., Keire, D.A., Xu, X., Chen, K. *Application of ultra-centrifugation and bench-top 19F NMR for measuring drug phase partitioning for the ophthalmic oil-in-water emulsion products*. AAPS Pharma Sci Tech (2018), 19(4):1647-1651. doi: 10.1208/s12249-018-0973-8.

Presentations

- Bellantone, R. *Pulsatile Microdialysis of Suspension and Emulsion Products*. Presentation at Public Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. White Oak, MD, Oct. 6, 2017.
- Hu, M. *Equivalence Testing of Complex Particle Size Distribution Profiles Based On Earth Mover's Distance*. Presentation at Complex Generic Drug Product Development Workshop. Silver Spring, MD, Sept. 12, 2018.
- Jiang, J. *An Overview of Challenges and Opportunities in the Development of Complex Generic Drug Products*. Presentation at DIA We- binar. Silver Spring, MD, Mar. 5, 2018.
- Kozak, D. *In Vitro Bioequivalence Testing for Topical Ophthalmic Suspension Products*. Presentation at Complex Generic Drug Product Development Workshop. Silver Spring, MD, Sept. 12, 2018.
- Kozak, D. *Introduction: Novel IVRT for Complex Formulations*. Presentation at Public Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. White Oak, MD, Oct. 6, 2017.
- Sailor, M. *In Vitro and In Vivo Characterization of Ophthalmic Suspensions*. Presentation at Public

Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. White Oak, MD, Oct. 6, 2017.

- Xu, X. *Dissecting Drug Release From Emulsions: A Balance Between Kinetics and Equilibrium*. Presentation at Controlled Release Society Annual Meeting, New York, NY, July 24, 2018.

Posters

- Bao, Q., Newman, B., Wang, Y., Choi, S., and Burgess, D. *In Vitro - Ex Vivo Correlation of Drug Release From Semisolid Ophthalmic Ointments*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Bao, Q., Shen, J., Newman, B., Wang, Y., Choi, S., and Burgess, D. *Impact of Excipient Sources On In Vitro Drug Release Characteristics of Semisolid Ophthalmic Ointments*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Sub- stances and Formulations. Silver Spring, MD, Oct. 6, 2017.
- Chen, L., Manna, S., Petrochenko, P., Wu, Y., Qin, B., Kozak, D., and Zheng, J. *Importance of Comparative Unit Dose Concentration in the Evaluation of Complex Ophthalmic Suspension Product Quality*. Poster Presentation at Controlled Release Society Annual Meeting. New York City, NY, July 22, 2018.
- Dong, Y., Hengst, L., Patel, D., Hunt, R., Qu, H., Choi, S., Ashraf, M., Cruz, C.N., Xu, X. *A Kinetic Approach to Determine Partitioning Coefficient*. Controlled Release Society Annual Meeting, New York, NY, July 22-24, 2018.
- Dong, Y., Qu, H., Hengst, L., Choi, S., Absar, M., Li, V., Zheng, J., Ashraf, M., Cruz, C., and Xu, X. *Bi-Phasic Mass Transfer and Trans- Membrane Diffusion in Emulsions*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.
- Dong, Y., Qu, H., Hengst, L., Choi, S., Absar, M., Li, V., Zheng, J., Ashraf, M., Cruz, C., and Xu, X. *Understanding Bi-Phasic Mass Transfer and Trans-Membrane Diffusion Kinetics in Emulsions*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Dong, Y., Qu, H., Pavurala, N., Wang, J., Martinez, M., Fahmy, R., Ashraf, M., Cruz, C., and Xu, X. *Effect of Formulation and Process Variables on the Properties of Cyclosporine Ophthalmic Ointments*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.
- Hadar, J., Garner, J., Skidmore, S., Park, K., Park, H., Kozak, D., and Wang, Y. *Correlation Analysis of Refractive Index (Dn/Dc) for Plgas with Different Ratios of Lactide to Glycolide.* Poster Presentation at Controlled Release Society Annual Meeting. New York City, NY, July 22, 2018.
- Hu, M., Jiang, X., Absar, M., Choi, S., Shen, M., Weng, Y., Zhao, L., and Lionberger, R. *A Statistical Bioequivalence Approach Based On Earth Mover's Distance for Equivalence Testing of Particle Size Distribution*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- 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.
- Petrochenko, P., Hu, P., Wu, Y., Choi, S., Kozak, D., and Zheng, J. *Physicochemical Characterization of Tobradex and Tobradex ST Un- der Physiological Conditions*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations.

Silver Spring, MD, Oct. 6, 2017.

- Qu, H., Wang, J., Wu, Y., Zheng, J., Yellela, K., Absar, M., Choi, S., Ashraf, M., Cruz, C., and Xu, X. *Asymmetric Flow Field Flow Fractionation As an Analytical Tool for the Size Based Separation and Characterization of Complex Ophthalmic Emulsions*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.
- 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.
- Wang, X., Patil, S., and Chen, K. *Novel Method for Bench-Top 19F NMR in Measuring API Phase Partition for Oil-in-Water Emulsion Drug Products*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.
- Wood, E., Tyner, K., *A Critical Evaluation of Emerging High Resolution Imaging Technologies for the Characterization of Complex Formulations*. Poster Presentation at the 2018 NIPTE Research Conference, Brooklyn, NY, Aug. 22-23, 2018.