FY2018 GDUFA Science and Research Report: Topical Dermatological 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: Topical Dermatological Drug Products (https://www.fda.gov/industry/generic-drug-user-fee-amendments/fy2015-regulatory-science-research-report-topical-dermatological-drug-products)
- FY2016 GDUFA Science and Research Report: Topical Dermatological Drug Products (https://www.fda.gov/industry/generic-drug-user-fee-amendments/fy2016-regulatory-science-report-topical-dermatological-drug-products)
- FYs 2013-2017 GDUFA Science and Research Report: Topical Dermatological Drug Products (https://www.fda.gov/industry/generic-drug-user-fee-amendments/office-generic-drugs-fys-2013-2017-regulatory-science-research-report)

Introduction

The goals of our research program in topical dermatological drug products are to explore and develop new in vitro (laboratory), in silico (computational modeling) and in vivo (human subject studies) approaches, which may be used to establish bioequivalence (BE) for topical products. The ultimate intent is to develop more efficient regulatory standards that generic drug applicants could use to demonstrate BE for prospective generic topical products. The expectation is that generic topical products could be efficiently developed and approved using the new approaches, thereby improving patient access to topical drug products.

Research

To achieve this goal, and to explore the general applicability of these new approaches with which to evaluate topical BE, the GDUFA research during FY2018 encompassed multiple different topical drugs and dosage forms. The results of this research elucidated how the qualitative (Q1) and quantitative (Q2) composition, as well as the physical and structural arrangement of matter in the dosage form (Q3), control the rate and extent to which topical drugs become available at the site of action . These results were confirmed in vitro and in vivo using novel approaches to evaluate the cutaneous pharmacokinetics (PK) of topical drugs. A technique known as an In Vitro Permeation Test (IVPT) was used to evaluate the cutaneous PK of metronidazole, lidocaine, and prilocaine, each from cream and gel products. The same metronidazole, lidocaine, and prilocaine cream and gel products were also evaluated in vivo, using dermal microdialysis (dMD) and/or dermal open flow microperfusion (dOFM) probes inserted into the skin. In addition, the cutaneous PK of lidocaine from a topical delivery system (patch) was also evaluated both, in vitro and in vivo.

Parallel, complementary in vitro research performed independently at the University of Mississippi and the University of South Australia characterized the physical and structural (Q3) properties of metronidazole, lidocaine, and prilocaine cream and gel products, and correlated these results with IVPT studies using the same products. The IVPT studies with these products were also performed at the University of Maryland (Baltimore). The metronidazole cream and gel products were also evaluated in vivo using dMD at Long Island University (Brooklyn), and the lidocaine and prilocaine cream and gel products were evaluated in vivo using dOFM at Joanneum Research (Austria).

Collectively, the results of the research with different drugs and drug products, using Q1, Q2 and Q3 characterization techniques, in vitro methodologies (e.g., IVPT), and in vivo techniques (dMD and dOFM), all performed in parallel by independent research groups, consistently demonstrated that products which are Q1 and Q2 the same, and Q3 similar, when compared to a reference listed drug (RLD) product, deliver topical drugs at the same rate and to the same extent as the RLD product. This work also consistently demonstrated that IVPT studies (**Figure 1**) are a sensitive and discriminating approach by which to evaluate the cutaneous PK of topical drugs. Of particular importance, this research illustrated the generalizability of the principles that influence BE for various topical drug products and supported the development of additional product-specific guidances which include an in vitro option by which to demonstrate BE.

The excised human skin that is used in IVPT experiments as the rate-controlling membrane to the permeation of compounds applied on the skin is an important factor for obtaining meaningful, biorelevant permeation data that has the potential to correlate with and be predictive of in vivo product performance. Yet, while IVPT studies have the benefit of providing biorelevant information, the inherent variability of these biological skin samples may limit the utility of IVPT studies as routine quality control tests. By contrast, synthetic membranes made of materials like cellulose acetate and polyethersulfone, which are utilized for in vitro release test (IVRT) experiments, have the advantage that they are generally consistent and provide reproducible results, making them potentially suitable as quality control tests. However, unlike IVPT studies with excised human skin, IVRT studies with synthetic membranes are not expected to correlate with or be predictive of in vivo product performance.

To develop an in vitro test that could be precise and reproducible as well as being biologically meaningful (biorelevant), we explored using genetically consistent, cultured (lab-grown) three-dimensional human skin membranes in an IVPT study. To evaluate the relative variability of the cultured skin compared to that of natural, excised human skin (prepared as either heat-separated epidermis (HSE) or dermatomed skin), each type of membrane was mounted in the same type of diffusion cell apparatus, and used to characterize the cutaneous PK of testosterone (as a model compound). The influence of different diffusion cell apparatus on the consistency of the permeation data was also assessed.

The results indicated that lab-cultured human skin preparations were typically less variable but more permeable than excised human (cadaver) skin preparations. Although cultured human skin preparations may provide lower sample-to-sample variability compared to excised human (cadaver) skin, the compromised barrier function of cultured skin (to testosterone permeation) currently appears to limit its usefulness for IVPT studies. Nonetheless, this is a promising area of research and development as a method that could potentially be biorelevant and may be suitable to monitor the quality and performance of topical or transdermal formulations over their shelf life or for certain scale-up and post-approval changes (SUPAC).

Additional research is in progress as part of a contract with QPS, LLC, using physical and structural (Q3) characterization studies, In Vitro Release Test (IVRT) studies, and IVPT studies that are intended to evaluate the comparability of AT-rated topical ointments. Also, in silico (computational modeling and simulation) research in progress is currently verifying the predictions of physiologically-based PK models by comparison with empirical datasets, including those described above. Additional internal FDA research related to the optimization of diffusion cell designs and the comparability of different types of skin membranes and diffusion devices for IVPT studies is currently in progress.

Figure 2. A Schematic Illustration of an IVPT Study.

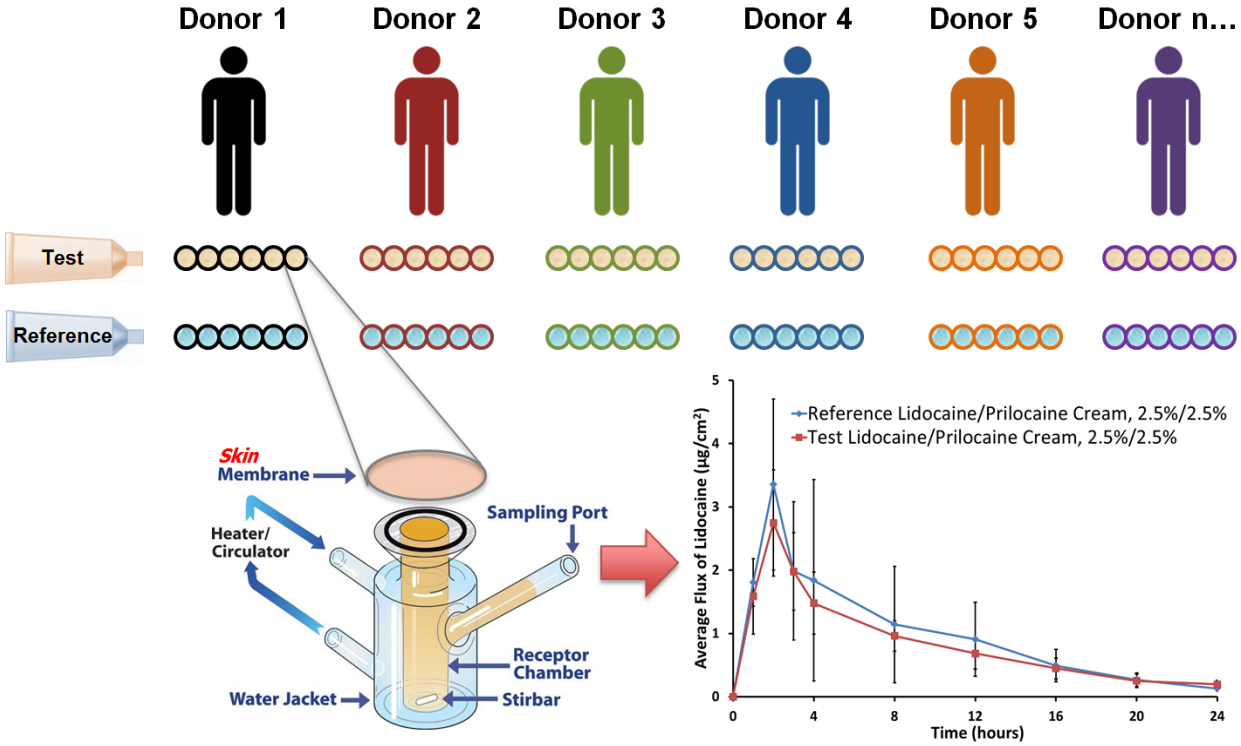

Figure 2: A schematic illustration of an IVPT study showing how sections of excised human skin from multiple donors are each mounted on diffusion cells in vitro and dosed with either the Test or the Reference topical drug product. The topical drug permeates through the skin into the solution in the receptor chamber, which is sampled at progressive time points to characterize the cutaneous PK of the drug. The diffusion cell shown in this diagram is a vertical (Franz) diffusion cell, although other types can be used. The cutaneous PK of lidocaine is shown in the inset PK profile, based upon six replicate skin sections from a single donor dosed with either the Reference (EMLA®) lidocaine/prilocaine cream, 2.5%;2.5% or a Test product, which is a generic version of EMLA® for which BE was originally established based upon a comparative clinical endpoint BE study.

Research Projects and Collaborations

New Grants and Contracts

- New Grant (U01FD006533) *Bioequivalence of Topical Products: Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products Using Non-Invasive Techniques* with Richard Guy at University of Bath
- New Grant (U01FD006521) *Characterize Skin Physiology Parameters Utilized in Dermal Physiologically-Based Pharmacokinetic Model Development Across Different Skin Disease States* with Sebastian Polak at Simcyp, Ltd.
- New Grant (U01FD006507) *Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations* with Sathyanarayana Murthy at University of Mississippi

- New Grant (U01FD006496) *Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations* with Michael Roberts at University of South Australia
- New Grant (U01FD006526) *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 (U01FD006522) *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

Continuing Grants and Contracts

- Active Grant (U01FD004947) *Bioequivalence of Topical Drug Products: In Vitro - In Vivo Correlations* with Audra L Stinchcomb at University of Maryland
- Active Grant (U01FD005226) *Characterization of Critical Quality Attributes for Semisolid Topical Drug Products* with Michael Roberts at University of South Australia
- Active Grant (U01FD005233) *Topical Products and Critical Quality Attributes* with Sathyanarayana Murthy at University of Mississippi
- Active Contract (HHSF223201610125C) *Assessment of the In Vitro Percutaneous Absorption, In Vitro Rate of Release, and Physicochemical Properties of Selected Commercially Available AT Rated Ointment Formulations* with Shanna Geigle at QPS, LLC
- Active Grant (U01FD005862) *Benchmark of Dermis Microdialysis to Assess Bioequivalence of Dermatological Topical Products* with Grazia Stagni at Long Island University
- Active Grant (U01FD005861) *Development of a Universal Bioequivalence Test Method for Topical Drugs Using dOFM* with Frank Sinner at Joanneum Research
- Active Grant (U01FD005232) *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 FDA Research

- *Snowflakes in Transdermal Systems: Influence of Drug Crystallization on Drug Permeation and Quality of TDS*
- *Performance comparison of permeation membranes and devices used in modern in vitro skin permeation test (IVPT) studies*
- *Computational Fluid Dynamics (CFD) Analysis of Spreadability of Topical Formulations*
- *Verification of IVRT method for AT-rated topical ointments*

Outcomes

Product-Specific Guidances

- *Revised Draft Guidance for Dapsone Topical Gel*. FDA Guidance Posting. Oct. 19, 2017. Link to Posting.
- *New Draft Guidance for Docosanol Topical Cream*. FDA Guidance Posting. Oct. 19, 2017. Link to Posting.

- *New Draft Guidance for Erythromycin Topical Gel*. FDA Guidance Posting. Oct. 19, 2017. Link to Posting.
- *New Draft Guidance for Ivermectin Topical Cream*. FDA Guidance Posting. Oct. 19, 2017. Link to Posting.
- *New Draft Guidance for Crisaborole Topical Ointment*. FDA Guidance Posting. Feb. 8, 2018. Link to Posting.
- *Revised Draft Guidance for Triamcinolone Acetonide Dental Paste*. FDA Guidance Posting. Feb. 8, 2018. Link to Posting.
- *New Draft Guidance for Fluocinolone Acetonide Topical Cream*. FDA Guidance Posting. July 20, 2018. Link to Posting.
- *New Draft Guidance for Efinaconazole Topical Solution*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.
- *New Draft Guidance for Ivermectin Topical Lotion*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.
- *New Draft Guidance for Luliconazole Topical Cream*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.
- *New Draft Guidance for Penciclovir Topical Cream*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.
- *Revised Draft Guidance for Tacrolimus Topical Ointment (0.03%)*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.
- *Revised Draft Guidance for Tacrolimus Topical Ointment (0.1%)*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.
- *New Draft Guidance for Tavaborole Topical Solution*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.

Publications

- Schimek, D., Raml, R., Francesconi, K. A., Bodenlenz, M., Sinnner, F. *Quantification of acyclovir in dermal interstitial fluid and human serum by ultra-high-performance liquid chromatography-high resolution tandem mass spectrometry for topical bioequivalence evaluation*. Biomedical Chromatography (2018) 32(6): e4194. doi: 10.1002/bmc.4194. PMID 29349796.
- Wittum, R., Naegel, A., Heisig, M., and Wittum, G. *Mathematical Modelling of the Viable Epidermis: Impact of the Cell Shape and Vertical Arrangement*. Mathematics and Mechanics of Solids. (2017): 1–14. doi:10.1177/1081286517743297.

Presentations

- Benson, H. *Correlation of Physicochemical Characteristics and In Vitro Permeation Test (IVPT) Results for Acyclovir Topical Products*. Presentation at Drug Delivery Australia. Wollongong, Australia, Oct. 23, 2017.
- Bunge, A. *Improved Stratum Corneum Sampling In Vivo Delivers Obvious value for Topical Bioequivalence Assessment*. Presentation at Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access. White Oak, MD, Oct. 20, 2017.
- Ghosh, P. *Understanding the Complexity of Topical (Dermatological) Semisolids*. Presentation at NIPTE Continuous Manufacturing and Development of Complex Generics. Brooklyn, NY, Aug. 24, 2018.

- Guy, R. H. *Improved Stratum Corneum Sampling In Vivo Delivers Obvious value for Topical Bioequivalence Assessment*. Presentation at Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access. White Oak, MD, Oct. 20, 2017.
- Guy, R. H. *Measuring Drug Concentration in the Skin In Vivo: Techniques and Challenges*. Presentation at American Association of Pharmaceutical Scientists Annual Meeting Workshop: Dermatological Drug Products: Developmental & Regulatory Considerations. San Diego, CA, Nov. 12, 2017.
- Lionberger, R. *GDUFA Regulatory Science Research and the Future of Generic Drugs*. Presentation at Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access. White Oak, MD, Oct. 20, 2017.
- Luke, M. *Drug Compounding and the Dermatologist*. Presentation at AAD 2018. San Diego, CA, Feb. 19, 2018.
- Luke, M. *Implications of Skin Anatomy, Skin (Patho-)Physiology, and Product Physico-Chemistry on FDA Regulatory Approach for Generic Dermatologic Products*. Presentation at 30th Anniversary Perspectives in Percutaneous Penetration Conference. La Grande Motte, France, Apr. 5, 2018.
- Murthy, S. N. *Advanced Characterization Approaches for Topical Formulations*. Presentation at American Association of Pharmaceutical Scientists Annual Meeting. San Diego, CA, Nov. 15, 2017.
- Murthy, S. N. *Characterizing the Critical Quality Attributes and In Vitro Bioavailability of Acyclovir and Metronidazole Topical Products.* Presentation at Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access. White Oak, MD, Oct. 20, 2017.
- Murthy, S. N. *Microstructural Characterization and In Vitro Permeation Testing of Topical Products*. Presentation at 5th Annual Transdermal & Intradermal Drug Delivery Systems 2018, Philadelphia, PA. Sept. 7, 2018.
- Patel, N. *Skin in the Game: Mechanistic Modeling of Dermal Drug Absorption*. Presentation at The Certara Blog: PBPK Modeling & Simulation. Mar. 2, 2018.
- Raney, S. *FDA Regulatory Initiatives Related to Generic Dermatological and Transdermal Drug Products*. Presentation at 30th Anniversary Perspectives in Percutaneous Penetration Conference. La Grande Motte, France, Apr. 5, 2018.
- Raney, S. *Strategies to Improve Patient Access to High Quality Topical Products*. Presentation at American Association of Pharmaceutical Scientists Annual Meeting Workshop: Dermatological Drug Products: Developmental & Regulatory Considerations. San Diego, CA, Nov. 12, 2017.
- Raney, S. *The Journey from Developing the Research Studies to Drafting a New Regulatory Standard: A Case Study with Acyclovir Cream*. Presentation at Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access. White Oak, MD, Oct. 20, 2017.
- Roberts, M. *Correlation of Physicochemical Characteristics and In Vitro Permeation Tests (IVPT) Results for Acyclovir and Metronidazole Topical Products*. Presentation at Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access. White Oak, MD, Oct. 20, 2017.
- Roberts, M. S. *Topical Semisolid Drug Product Critical Quality Attributes (Q3 Characterization) with Relevance to Topical Bioequivalence*. Presentation at Fifteenth International Conference on Perspectives in Percutaneous Penetration. La Grande Motte, France, Apr. 5, 2018.
- Sinner, F. *Clinical Pharmacokinetic Evaluation of Dermal Bioavailability and Bioequivalence*. Presentation at American Association of Pharmaceutical Scientists Annual Meeting Workshop: Dermatological Drug Products: Developmental & Regulatory Considerations. San Diego, CA, Nov. 12, 2017.

- Sinner, F. *In Vivo Dermal Open Flow Microperfusion: A Novel Approach to Evaluating Topical Bioavailability and Bioequivalence*. Presentation at Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access. White Oak, MD, Oct. 20, 2017.
- Stinchcomb, A. *Characterizing In Vitro Bioavailability of Acyclovir and Metronidazole Topical Products, and In Vitro-In Vivo Correlation Results with Transdermal Systems*. Presentation at Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access. White Oak, MD, Oct. 20, 2017.

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., 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.
- 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.
- Ajjarapu, S., Rangappa, S., DeBoyace, K., Wildfong, P., and Murthy, S. *Metronidazole Crystal Patterns Formed During the Metamorphosis of Topical Carbopol Gels*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Ajjarapu, S., Rangappa, S., Ghosh, P., Raney, S., and Murthy, S. *A Novel Strategy for the Efficient Modulation of Topical Drug Delivery to Validate the Sensitivity of an In Vitro Permeation Test (IVPT)*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- 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.
- Jung, N., Namjoshi, S., Mohammed, Y., Grice, J., Raney, S., Roberts, M., and Windbergs, M. *Evaluation of Penetration Kinetics of Commercial Topical Formulations in Human Skin Using Non-Invasive Confocal Raman Microscopy*. Poster Presentation at International Conference and Workshop on Biological Barriers. Sept. 27, 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.
- 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.
- Patel, N. and Polar, S. *Development of the Dermal Absorption Model for the Ketoprofen Local and Systemic Exposure Prediction*. June 20, 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.

- Rangappa, S., Ajjarapu, S., Ghosh, P., Raney, S., and Murthy, S. *Evaluation of Different Dose Application Techniques on the In Vitro Cutaneous Pharmacokinetics of Metronidazole From Topical Gel and Cream Products*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Rangappa, S., Ajjarapu, S., Hashemnejad, S., Prado, R., Ghosh, P., Raney, S., Kundu, S., Murthy, and SN. *Correlation Between the Quality Attributes and Performance Characteristics of Metronidazole Gels and Creams: Implications for the Evaluation of Bioequivalence*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Sharma, P., Srinatha, A., Raney, S., Ghosh, P., Hashemnejad, S., Kundu, S., Repka, M., and Murthy, S. *The Systematic Influence of Changes in Manufacturing Process Variables on the Microstructure and Performance of Topical Emulsions*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Shukla, S., Thomas, S., Hammell, D., Bunge, A., Hassan, H., and Stinchcomb, A. *In Vivo Evaluation of Lidocaine Bioavailability from Two Topical Patch Products by Pharmacokinetic and Skin (Tape) Stripping Analyses*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Tiffner, K., Bodenlenz, M., Raml, R., Raney, S., Sinner, F., Augustin, T., and Birngruber, T. *Variability of Topical Penetration Data: What Do We Learn From a BE-Study Using Dermal Open Flow Microperfusion*. Poster Presentation at Perspective in Percutaneous Penetration. La Grande Motte, France, Apr. 3, 2018.
- Tiffner, K., Bodenlenz, M., Schimek, D., Reisenegger, P., Rantou, E., Raml, R., Raney, S., and Sinner, F. *Bioequivalence of Topical Products in Excised Human Skin Assessed with Dermal Open Flow Microperfusion (dOFM)*. Poster Presentation at Perspective in Percutaneous Penetration. La Grande Motte, France, Apr. 3, 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.
- Zhang, Q., Ghosh, P., Raney, S., Hammell, D., Hassan, H., and Stinchcomb, A. *Characterization of the Cutaneous Pharmacokinetics of Three Metronidazole Topical Drug Products Evaluated by an In Vitro Permeation Test (IVPT) with Excised Human Skin*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.