FY2018 GDUFA Science and Research Report: Long-Acting Injectables and Implants

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

- FY2016 GDUFA Science and Research Report: Long-Acting Injectable Formulations (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549166.htm)
- FYs 2013-2017 GDUFA Science and Research Report: Long-Acting Injectables and Implants (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm597035.htm)

Introduction

Our research on long-acting injectables (LAI) and implants is targeted on providing a scientific foundation for the efficient development of generic competition in this product category. In FY18, there were 15 active research projects on long-acting injectables and implants including nine grants and five contracts as well as one internal project. The focus of these projects are: 1) to explore biorelevant in vitro-in vivo correlations (IVIVCs) for biodegradable injectable poly lactide-co-glycolide (PLGA) microspheres; 2) to investigate dissolution methods for LAI drug products including PLGA microspheres and implants and multivesicular liposomes (MVLs); 3) to obtain a better understanding of the impact of properties of PLGA polymers on product performance; 4) to develop modeling tools to facilitate development of generic LAI formulation development as well as bioequivalence guidances for LAI formulations; 5) to investigate potential peptide PLGA interactions during product manufacturing and use; 6) to develop analytical method for separating PLGA polymers when used in mixture; and, 7) to develop methods for fully characterizing structure of branched PLGA polymers.

Research

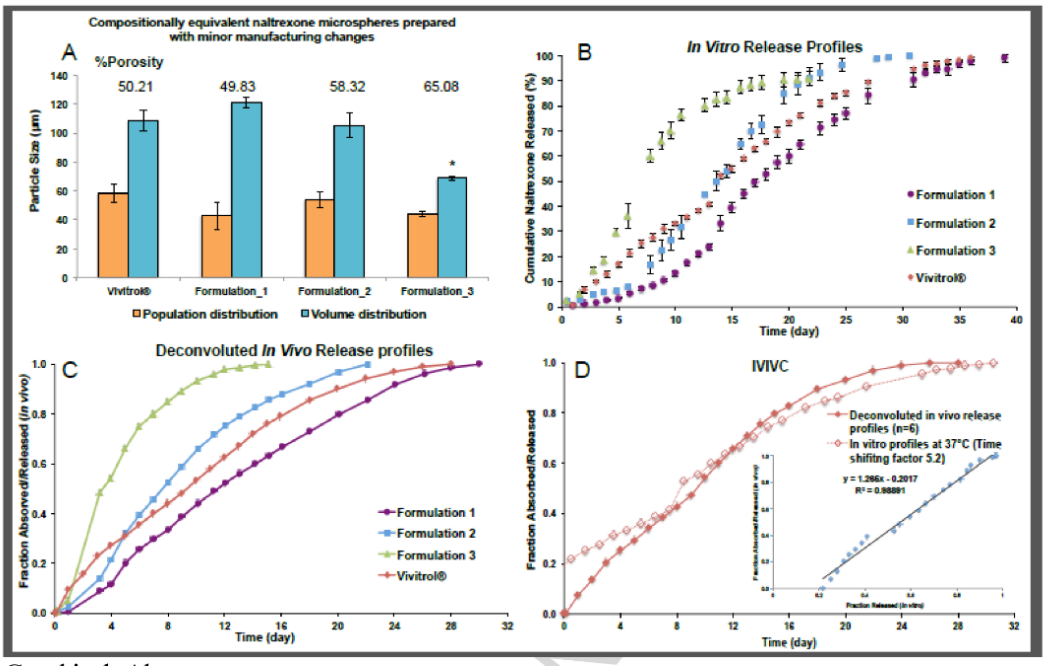
All projects have made significant progress. Here are some highlights:

1) An IVIVC has been established for naltrexone microspheres using a rabbit model (**Figure 1**). All in-house prepared formulations were compositionally equivalent with manufacturing differences. Vivitrol® was also evaluated in the study. The developed IVRT method was able to discriminate the formulations with differences in physicochemical properties.

2) Interactions between various solvents and PLGA polymers with similar molecular weight, but different L/G ratios were investigated. **Figure 2** shows PLGA solubility in various solvents at 30^{o}C. The information on PLGA solubility in various solvents will be helpful for understanding effects of solvent on formulation development as well as polymer characterization.

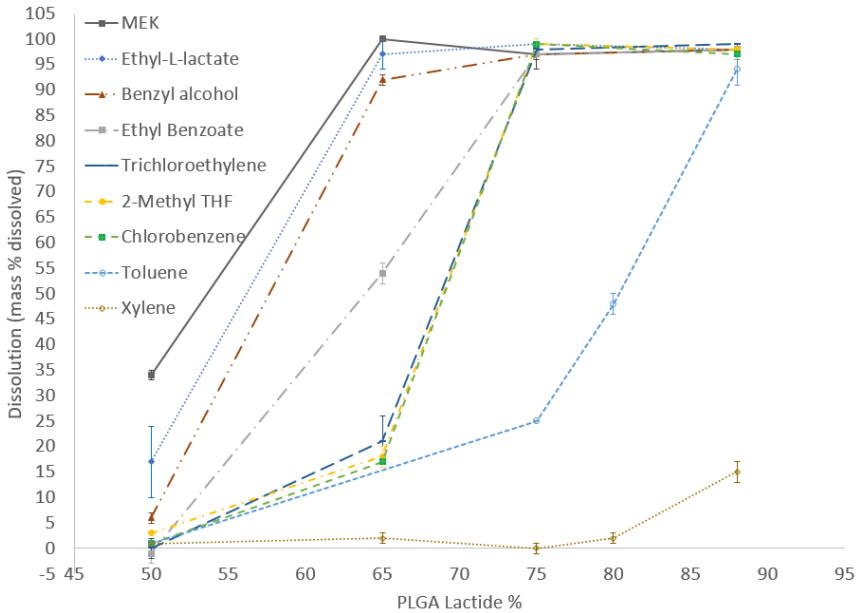
3) A novel IVRT method for assessing in vitro drug release profile of MVLs using USP Apparatus II coupled with in-line continuous UV monitoring has been developed. A tri-phasic release characteristic was observed under all testing conditions, comprised of an initial burst release, lag phase, and a secondary release. Compared to conventional sample-and-separate method based on water shaker, this method could be a better tool to obtain mechanistic understanding of drug release from MVLs.

Figure 1. Graphical abstract "Development of In Vitro-In Vivo Correlation of Parenteral Naltrexone Loaded Polymeric Microspheres".[1]



A: Mean Particle size ± SD of all the tested formulations. B: In vitro drug release profiles of all the tested formulations. C: Deconvoluted in vivo drug release profiles. D: IVIVC.

Figure 2. PLGA Solubility in Various Solvents at 30°C.



[1] https://www.sciencedirect.com/science/article/pii/S0168365917305096?via%3Dihub#f0040

Research Projects and Collaborations

New Grants and Contracts

- New Contract (HHSF223201810115C) *Impact of Polymer Source Variations on Parenteral Microsphere Drug Product Performance* with Diane J Burgess at University of Connecticut, Department of Pharmaceutical Sciences
- New Contract (HHSF223201810187C) *Influence of Raw Materials, Manufacturing Variables, and Storage Conditions on In Vitro and In Vivo Performance of Exenatide in PLGA Microspheres* with Steven Schwendeman at the University of Michigan, College of Pharmacy

Continuing Grants and Contracts

- Active Grant (1U01FD004931) *In Vitro In Vivo Correlations of Parenteral Microsphere Drug Products* with Diane J Burgess at University of Connecticut
- Active Grant (1U01FD005169) *Dissolution Methods for Parenteral Sustained Release Implant Drug Products* with Diane J Burgess at University of Connecticut
- Active Contract (HHSF223201510102C) *Computational Drug Delivery: Leveraging Predictive Models to Develop Bioequivalent Generic Long Acting Injections* with Sam Rothstein at Qrono, Inc.
- Active Grant (1U01FD005442) *Pharmacometric Modeling and Simulation for Evaluation of Bioequivalence for Leuprolide Acetate Injection* with Catherine Mary, Turner Sherwin at University of Utah
- Active Grant (1U01FD005444) *Data-Fusion Based Platform Development of Population PKPD Modeling and Statistical Analysis for Bioequivalence Assessment of Long-Acting Injectable Products* with Seongkyu Yoon at University of Massachusetts
- Active Grant (1U01FD005463) *Development of PBPK Simulation for Long-Acting Injectable Microspheres* with Viera Lukacova at Simulations Plus
- Active Grant (1U01FD005446) *Development of a Dissolution Method for Long-Acting Periodontal Drug Products* with Kevin S Li at University of Cincinnati
- Active Grant (1U01FD005447) *Biorelevant Dissolution Methods for Particulate Dosage Forms in the Periodontal Pocket* with Lisa C Rohan at Magee-Women's Research Institute and Foundation
- Active Grant (1U01FD005443) *Development of Real-Time and Accelerated Dissolution Methods for a Long-Acting Levonorgestrel Intrauterine System* with Diane J Burgess at University of Connecticut
- Active Contract (HHSF223201510170C) *Influence of Raw Materials, Manufacturing Variables, and Storage Conditions on Release Performance of Long Acting Release Microsphere Products* with Steven Schwendeman at University of Michigan
- Active Grant (1U01FD005847) *Investigation of Peptide-Polymer Interactions in PLGA Microspheres* with Steven Schwendeman at University of Michigan
- Active Contract (HHSF223201610091C) *Advanced Analytical Techniques for Mixed Polymer Drug-Delivery Systems* with Kinam Park at Akina, Inc.
- Active Contract (HHSF223201710123C) *Development of Analysis Technique for Structural Characterization of Star-Shaped Polyesters Used for Drug Delivery* with Kinam Park at Akina, Inc.
- Active Contract (HHSF223201710135C) *In-Vitro In-Vivo Correlation of the Long-Acting Injectable Suspensions Improve Scientific Approaches to Evaluate Generic Drugs* with Diane J Burgess at University of Connecticut

Active FDA Research

- *Bupivicaine Multivesicle Liposomes*

Outcomes

Product Specific Guidances

- *New Draft Guidance for Bupivacaine Injection Injectable, Liposomal*. FDA Guidance Posting. Feb. 8, 2018. Link to Posting.
- *New Draft Guidance for Leuprolide Acetate; Norethindrone Acetate Intramuscular; Oral Injectable; Tablet*. FDA Guidance Posting. Feb. 8, 2018. Link to Posting.

Publications

- Beekman, C., Matta, M., Thomas, C., Mohammad, A., Stewart, S.,Xu, L., Chockalingam, A., Shea, K., Sun, D., Jiang, W., Patel, V., and Rouse, R. *Comparative Evaluation of US Brand and Generic Intravenous Sodium Ferric Gluconate Complex in Sucrose Injection: Biodistribution After Intravenous Dosing in Rats*. Nanomaterials. (2018) **8**(1):10. doi: 10.3390/nano8010010. PMID: 29283393.
- Garner, J., Skidmore, S., Park, H., Park, K., Choi, S., and Wang, Y. *Beyond Q1/Q2: The Impact of Manufacturing Conditions and Test Methods on Drug Release From PLGA-Based Microparticle Depot Formulations*. J Pharm Sci. (2018) **107**(1):353–361. doi: 10.1016/j.xphs. 2017.10.027. PMID: 29107048.

Presentations

- Burgess, D. *In Vitro Drug Release from Complex Parenterals and Development of IVIVCs*. Presentation at Public Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. White Oak, MD, Oct. 6, 2017.
- Kinam, P. *Demonstrating Equivalence of Generic Complex Drug Substances and Formulations: Advances in Characterization and In Vitro Testing*. Presentation at Public Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. White Oak, MD, Oct. 6, 2017.
- Schwendeman, S. *Formulation Characterization of PLGA Microspheres*. Presentation at Public Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. White Oak, MD, Oct. 6, 2017.
- Sharan, S. *Evaluation of Residual Levonorgestrel As Potential Bioequivalence Metric for A Long Acting Intrauterine System Using Quantitative Modeling and Simulation Approach*. Presentation at American Association of Pharmaceutical Scientists Webinar. Webinar, MD, Oct. 12, 2017.
- Jiang, J. *An Overview of Challenges and Opportunities in the Development of Complex Generic Drug Products*. Presentation at DIA Webinar. Silver Spring, MD, Mar. 5, 2018.
- Manna, S. *Liposomes: Physicochemical Characterization and In Vitro Drug Release Testing*. Presentation at Complex Generic Drug Product Development Workshop. Silver Spring, MD, Sept. 12, 2018.
- Sharan, S. *Application of Modeling and Simulation in Establishing Appropriate Bioequivalence Limits for Complex Formulations*. Presentation at Complex Generic Drug Product Development Workshop. Silver Spring, MD, Sept. 12, 2018.
- Qin, B. *Considerations for Establishing Q1/Q2 Sameness of Complex Formulations*. Presentation at Complex Generic Drug Product Development Workshop. Silver Spring, MD, Sept. 12, 2018.

Poster Presentations

- Andhariya, JV., Shen, J., Zou, Y., Wang, Y., Choi, S., and Burgess, D. *Development of In Vitro-In Vivo Correlation of Parenteral Naltrexone Loaded Polymeric Microspheres*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.
- Andhariya, JV., Shen, J., Zou, Y., Wang, Y., Choi, S., and Burgess, D. *Effect of Manufacturing Processes on Critical Quality Attributes of Peptide Microspheres*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Andhariya, JV., Zou, Y., Wang, Y., Choi, S., and Burgess, D. *Effect of Manufacturing Processes on Burst Release of Risperidone Microspheres*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Andhariya, JV., Shen, Y, Z., S, C., Y, W., and DJ, B. *Effect of Manufacturing Difference on the Drug Release Characteristics of Peptide Microspheres*. Poster Presentation at Controlled Release Society Annual Meeting. New York City, NY, July 22, 2018.
- Andhariya, JV., R, J., J, S., Y, Z., S, C., Y, W., and DJ, B. *Evaluation of Effect of Minor Manufacturing Changes and Establishment of IVIVC for Compositionally Equivalent Parenteral Microsphere Drug Products*. Poster Presentation at GPEN 2018. Singapore, Singapore, Sept. 26, 2018.
- Bao, Q., Gu, B., Price, C., Zou, Y., Wang, Y., Choi, S., and Burgess, D. *In Vitro Release Testing of Long-Acting Levonorgestrel Intrauterine System*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.
- Bao, Q., Gu, B., Price, C., Zou, Y., Wang, Y., Choi, S., and Burgess, D. *In Vitro Release Testing of Long-Acting Levonorgestrel Intrauterine System*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Bao, Q., Zou, Y., Wang, Y., Kozak, D., Choi, S., and Burgess, D. *Accelerated Drug Release Method for Long-Acting Levonorgestrel Intrauterine Systems*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Beig, A., Hong, J., Feng, L., Chang, R., Zhou, J., Ackermann, R., and Schwendeman, S. *PLGA-Peptide Interactions Relevant for Octreotide Loaded PLGA Microspheres*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.
- Garner, J., Skidmore, S., Hadar, J., Park, K., Park, H., Choi, S., and Wang, Y. *Assay of PLGA Types in Microparticle Depo Formulations*. 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., Choi, S., and Wang, Y. *The Effect of Lactide:Glycolide Ratio On PLGA Solubility in Selective Solvents*. 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, H., Park, K., Kozak, D., and Wang, Y. *Solvent-Dependent PLGA Solubility for Separation of Plgas with Different L:G Ratios*. Poster Presentation at Controlled Release Society Annual Meeting. New York City, NY, July 22, 2018.
- 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.
- Manna, S., Petrochenko, P., Wu, Y., Dong, Y., Koo, B., Chen, L., Ren, K., Oktem, B., Choi, S., Xu, X., Kozak, D., Wang, Y., and Zheng, J. *Assessing In Vitro Drug Release from Multivesicular Liposome: Comparison of Reverse Dialysis and Rotary Shaking Methods*. Poster Presentation at FDA Workshop:

Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.

- Manna, S., Petrochenko, P., Wu, Y., Koo, B., Ren, K., Chen, L., Dong, Y., Xu, X., Choi, S., Kozak, D., Wang, Y., and Zheng, J. *Assessing In Vitro Drug Release from Multivesicular Liposome: Comparison of Reverse Dialysis and Rotary Shaking Methods*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Manna, S., Petrochenko, P., Wu, Y., Koo, B., Ren, K., Chen, L., Dong, Y., Xu, X., Choi, S., Kozak, D., Wang, Y., and Zheng, J. *Probing Mechanism of Drug Release from Multivesicular Liposomes*. Poster Presentation at Controlled Release Society Annual Meeting. New York City, NY, July 23, 2018.
- Manna, S., Petrochenko, P., Wu, Y., Dong, Y., Koo, B., Chen, L., Ren,K., Oktem, B., Choi, S., Xu, X., Kozak, D., Wang, Y., and Zheng, J. *Developing Physicochemical Characterization and In Vitro Release Test Methods to Probe Drug Release Mechanism From Multivesicular Liposomes*. Poster Presentation at Microscopy and Microanalysis Annual Meeting. Baltimore, MD, Aug. 6, 2018.
- Patel, S., Greene, A., MacPherson, J., Basha, I., Desai, S., Zou, Y., Sfeir, C., Rothstein, S., Little, S., and Rohan, L. *Design, Fabrication, and Evaluation of a Small Volume Biorelevant Dissolution Apparatus for Extended-Release Periodontal Microparticles*. Poster Presentation at Controlled Release Society Annual Meeting. New York City, NY, July 18, 2018.
- Shahraz et al. *Development of In Vitro-in-Vivo Correlation for Long Acting Injectable Microsphere Formulations*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Prokash et al. *Data-Fusion Based Platform for Comparing Pharmacokinetics of Long-Acting Injectable Products*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Skidmore, S., Garner, J., Park, K., Park, H., Choi, S., and Wang, Y. *The Impact of In Vitro Test Methods on Drug Release from PLGA Microparticles*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.
- Suh, M., Kastellorizios, M., Zou, Y., Wang, Y., Choi, S., and Burgess, D. *Formulation and Microstructural in in Situ Forming Implants: In Vitro and In Vivo*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.
- Suh, M., Kastellorizios, M., Zou, Y., Wang, Y., Choi, S., and Burgess,D. *Effect of Polymer Characteristics on Formation of in Situ Forming Implants in Subcutaneous Tissue*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Zhou, J., Hirota, K., Ackermann, R., Walker, J., Wang, Y., Choi, S., Schwendeman, A., and Schwendeman, S. *Reverse Engineering of the 1-Month Lupron Depot and Development of Q1/Q2 Formulations*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.
- Zhou, J., Hirota, K., Feng, M., Doty, A., Olsen, K., Ackermann, R., Wang, Y., Choi, S., Schwendeman, A., and Schwendeman, S. *In Vitro In Vivo Correlation of Leuprolide Acetate-Loaded PLGA Microspheres*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Zhou, J., Walker, J., Ackermann, R., Olsen, K., Hong, J., Wang, Y., Jiang, X., Schwendeman, A., and Schwendeman, S. *Development and Characterization of Composition-Equivalent Formulations to the One- Month Lupron Depot*. Poster Presentation at Controlled Release Society Annual Meeting. New York City, NY, July 22, 2018.