FY2018 Regulatory Science 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:


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 collaboration. 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 process. 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°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”.

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

Figure 2. PLGA Solubility in Various Solvents at 30⁰C.

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 Polysters 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 Michigan
Active FDA Lab Collaborations

- *Bupivicaine Multivesicle Liposomes* with CDRH

Outcomes

Product Specific Guidance


Publications


Presentations


- Sharan, S. *Application of Modeling and Simulation in Establishing Appropriate Bioequivalence Limits*


**Poster Presentations**


- 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


