FY2018 GDUFA Science and Research Report: Complex Injectables, Formulations and Nanomaterials

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: Nanotechnology: Physiochemical Characterization of Nano-Sized Drug Products (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm503039.htm)
- FY2015 GDUFA Science and Research Report: Nanotechnology: Nano Drug Products: Clinical Pharmacology and In Vivo Correlation (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm512498.htm)
- FY2016 GDUFA Science and Research Report: Nanotechnology: Physiochemical Characterization of Nano-Sized Drug Products (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549163.htm)
- FYs 2013-2017 GDUFA Science and Research Report: Drug Products that Incorporate Nanotechnology (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm597035.htm)

Introduction

Drug products that contain nanomaterials are complex products manufactured to contain formulation elements within the nanoscale (e.g., sub-micron). The inclusion of nanomaterials within a drug product may enhance product performance compared to other products. These complex drug products can include, but are not limited to, emulsions, liposomes, and iron colloids. Although they represent less than 1% of all approved drug products, they are generally considered critical and high value products, accounting for over $15 billion in sales for 2017, and for which there are few approved generics available. The tools and best methods to manufacture and characterize these products is challenging due to the inherent complexity of the formulations.

Research

To assist both generic drug industry's development and FDA regulatory review of these complex products, several research projects have been conducted under GDUFA I and continue to be a research priority under GDUFA II. In FY2018, there were twelve active research projects on drug products that contain nanomaterials including two grants, one contract, and nine internal studies. The focus of these active projects is to develop and test: 1) new more sensitive and reproducible methodologies for measuring the pharmacokinetics of these complex products to improve in vivo bioequivalence (BE) study design; 2) a quality by design approach to elucidate the critical process parameters (CPP) that affect the critical quality attributes (CQA) of complex liposomal products; and 3) new high resolution imaging and spectroscopic methods for assessing and comparing the nanoscale structural features of these complex products.

Inter-Agency Agreement IAA-224-16-30015 is an ongoing project awarded to Dr. Stephane Stern at the National Cancer Institute's National Characterization Laboratory testing a new methodology, based on stable isotope dilution, to measure the amount of encapsulated and unencapsulated drug in complex formulations. Two complex drug products, liposomal doxorubicin and protein bound paclitaxel particles, are being studied as current analytical methods for measuring the encapsulated and unencapsulated amount of drug have high variability. The deuterated drug isotope acts as an internal control for formulation-induced changes improving

the measurement precision, and thereby reducing the number of human subjects required to conduct the in vivo BE study.

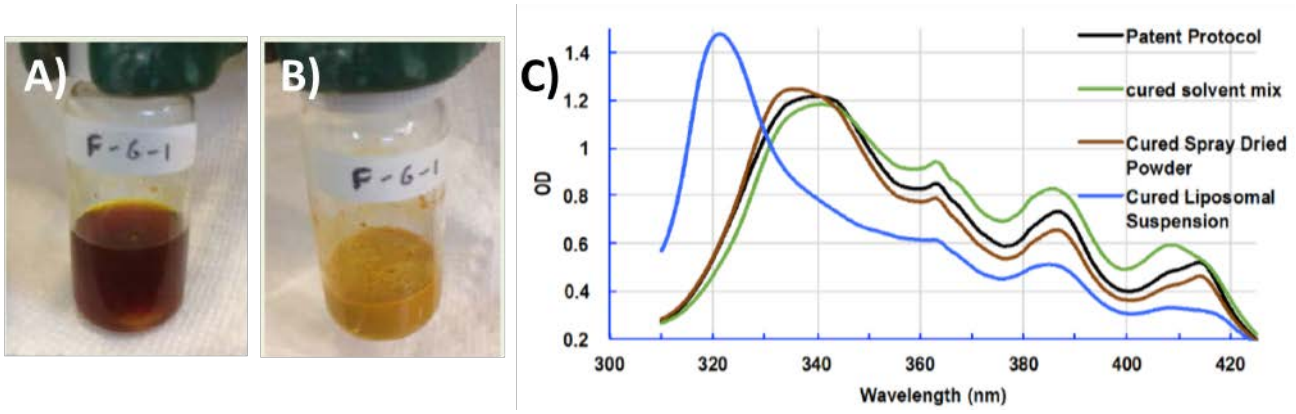
Grant 5U01FD005266 is an ongoing project awarded to Dr. Sarah Michel at the University of Maryland, Baltimore on September 10, 2014 that is comparing plasma total iron (TI), transferrin bound iron (TBI), non-transferrin bound iron (NTBI), and oxidative stress levels after IV administration of two sodium ferric gluconate products, an approved generic and the brand name reference, in healthy subjects using a crossover design. We are evaluating the feasibility of crossover design as it has the advantage of reducing study variability and further the number of required subjects, compared to the current recommended parallel BE study design.

Contract HHSF223201610093C was awarded to Dr. Alex Nivorozhkin at Neo-Advent Technologies, Inc. to evaluate manufacturing CPP's effect on the CQAs of liposomal amphotericin B products. In addition, they developed and evaluated new analytical methods to measure changes in these CQAs. The study showed that changing the formulation steps and/or manufacturing temperature played an important role in the incorporation of amphotericin B drug substance into the liposome as demonstrated by a UV-Vis spectra peak shift and reduced product toxicity (**Figure 1**). Results from this study will guide industry in their development of generic amphotericin B liposome products and aid FDA reviewers in their understanding of key product manufacturing steps that may affect overall product quality.

Two internal studies were undertaken to evaluate the sensitivity and potential use of new high-resolution imaging and sizing methods for characterizing the nanoscale properties of liposomal and emulsion products. Cryo-electron microscopy (cryo-EM) was evaluated as a potential regulatory tool to characterize the morphological properties of various complex drug products and to support demonstration of structural sameness between two purported similar products. Cryo-EM can directly image the globule/particle size distribution, shape, internal structure, agglomeration tendency, and surface features on the nanometer scale. As shown in **Figure 2**, the high-resolution single particle imaging capabilities of Cryo-EM demonstrated that a simple emulsion product contains a range of coexisting structural features including nanoemulsion droplets, liposomes, and emulsion-liposome aggregates. In the other internal study, the analytical capabilities and limitations of two commercially available instruments, tunable resistive pulse sensing (TRPS) and particle tracking analysis (PTA), were tested and compared to an in-house built microfluidic slit device. Compared to the higher accuracy, resolution, and larger analytical range of TRPS, PTA nanoparticle concentration measurements were more precise and reproducible. Testing the analytical capabilities of the microfluid slit is ongoing.

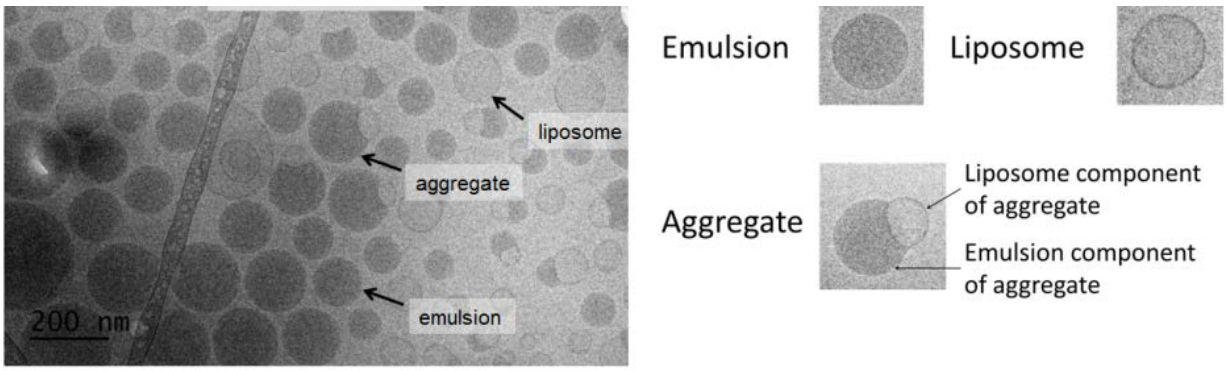
Additional internal research projects focus on testing of approved liposomal doxorubicin products and developing new analytical tools to characterize formulation components of lipid-based products. A capillary electrophoresis method with UV-Vis detection was developed for simultaneous separation and quantification of unencapsulated drug from the encapsulated drug in doxorubicin HCl liposomes.

Figure 1. Assessing the Critical Process Parameters and Critical Quality Attributes of Liposomal Amphotericin B.



Visual difference observed in amphotericin B solutions formed by altering the initial ingredient addition formulation steps to form A) a desired homogenous solution, or B) inhomogeneous aggregated suspension. C) UV-Spectra shift associated with amphotericin B distribution into the liposome bilayer observed in the final manufactured product when heat cured at the liposome stage. Heat curing at early steps does not affect this CQA of the product. Adapted from Nivorozhkin A; Liposomal Formulations of Amphotericin B; FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations, October 6, 2017.

Figure 2. Cryogenic Transmission Electron Microscopy Imaging of a Complex Emulsion Formulation.



Cryogenic transmission electron microscopy of oil droplets, liposomes, and liposome-oil droplet aggregates in a propofol emulsion product. Adapted from Wu Y, Petrochenko P, Koo B, Manna S, Myung JH, Choi S, Kozak D, Zheng J. Distinguish Coexistence of Nanoemulsion and Liposome in Propofol by Cryogenic Transmission Electron Microscopy. Microscopy and Microanalysis Annual Meeting, 2017.

Research Projects and Collaborations

Continuing Grants and Contracts

- Active Grant (1U01FD005206) *Physiologically Based Pharmacokinetic Model for Drugs Encapsulated into Liposomes* with Yanguang Cao at University of Buffalo
- Active Grant (1U01FD005266) *Evaluation of Iron Species in Healthy Subjects Treated with Generic and Reference Sodium Ferric Gluconate* with Sarah L Michel at University of Maryland
- Active IAA (IAA-224-16-3001S) *Novel Method to Evaluate Bioequivalence of Nanomedicines* with N/A at Nanotechnology Characterization Lab

Active FDA Research

- *Physicochemical Characterization of Protein-Particle Nanotechnology Drug Products*
- *In Vivo Biodistribution and In Vitro Characterization of Iron Colloid Drug Products*
- *In Vivo Biodistribution Evaluation of Liposome Drug Products*
- *Physicochemical Characterization of Soft Nanomaterials*
- *Assessing New Analytical Methods for Characterizing Characterization of Complex Nanotechnology Drug Products*
- *Bupivacaine Multi-vesicular Liposomes*
- *In Vitro Performance Characterizations of Sucroferric Oxyhydroxide to Establish Bioequivalence Methods*
- *Development of the Earth Movers Distance for Particle Size Distribution Comparisons*
- *Coupling Chemical Analysis to High Resolution Microscopy Methods for Enhanced Physicochemical Characterization of Drug Products Containing Nanomaterials and Other Complex Formulations*

Outcomes

Product-Specific Guidances

- *New Draft Guidance for Dantrolene Sodium Intravenous Powder for Suspension*. FDA Guidance Posting. Oct. 19, 2017. Link to Posting.
- *New Draft Guidance for Bupivacaine Injection Injectable, Liposomal*. FDA Guidance Posting. Feb. 8, 2018. Link to Posting.
- *Revised Draft Guidance for Triamcinolone Acetonide Injection Suspension*. FDA Guidance Posting. July 20, 2018. Link to Posting.
- *Revised Draft Guidance for Doxorubicin Hydrochloride Injection Injectable, Liposomal*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.
- *New Draft Guidance for Perflutren Injection Injectable, Liposomal*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.
- *New Draft Guidance for Sulfur Hexafluoride Lipid-Type A Microspheres Intravenous Injectable Suspension*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.

Publications

- Ansar, S., Jiang, W., and Mudalige, T. *Direct Quantification of Unencapsulated Doxorubicin in Liposomal Doxorubicin Formulations Using Capillary Electrophoresis*. Int J Pharm. (2018) **549**(1-2):109–114. doi: 10.1016/j.ijpharm.2018.07.019. PMID: 29981410.
- 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 Intra venous Sodium Ferric Gluconate Complex in Sucrose Injection: Biodistribution After Intravenous Dosing in Rats*. Nanomaterials. (2018) **8**(1):10. doi: 10.3390/nano8010010. PMID: 29283393.
- He, H., Liu, C., Wu, Y., Zhang, X., Fan, J., and Cao, Y. *A Multiscale Physiologically-Based Pharmacokinetic Model for Doxorubicin to Explore Its Mechanisms of Cytotoxicity and Cardiotoxicity in Human Physiological Contexts*. Pharm Res. (2018) **35**(9):174. doi: 10.1007/ s11095-018-2456-8. PMID: 29987398.
- 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.

- Pai, A. B., Pai, P. P., Meyer, D. E., Bales, B. C., Cotero, V. E., Zheng, N., and Jiang, W. *In Vitro and In Vivo DFO-Chelatable Labile Iron Release Profiles Among Commercially Available Intravenous Iron Nanoparticle Formulations*. Regulatory Toxicology and Pharmacology. (2018) **97**:17–23. doi: 10.1111/cts.12443. PMID: 29857115.
- Patil, S. M., Li, V., Peng, J., Kozak D., Xu, J., Cai, B., Keire, D. A. & Chen, K. . 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.
- Sun, D., Rouse, R., Patel, V., Wu, Y., Zheng, J., Karmakar, A., Patri, A., Chitranshi, P., Keire, D., Ma, J., and Jiang, W. *Comparative Evaluation of US Brand and Generic Intravenous Sodium Ferric Gluconate Complex in Sucrose Injection: Physicochemical Characterization*. Nanomaterials. (2018) **8**(1):25. doi: 10.1007/s40263-016-0332-9.
- Wu, M., Sun, D., Tyner, K., Jiang, W., and Rouse, R. *Comparative Evaluation of US Brand and Generic Intravenous Sodium Ferric Gluconate Complex in Sucrose Injection: In Vitro Cellular Uptake*. Nanomaterials. (2017) **7**(12):451. doi: 10.3390/nano7120451. PMID: 29244729.

Presentations

- Nivorozhkin, A. *Liposomal Formulations of Amphotericin B*. Presentation at Public Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. White Oak, MD, Oct. 6, 2017.
- Stern, S. *Nanomedicine Pharmacokinetics and Bioanalytical Methods to Measure Drug Release*. Presentation at 11th World Drug Delivery Summit. Baltimore, MD, Oct. 16, 2017.
- Jiang, W. *Excipients in Parenteral Drug Products*. Presentation at Forum of Complex Injectable Product Development. Zhuhai, China, Mar. 14, 2018.
- Jiang, W. Presentation at GBHI conference. Amsterdam, Netherlands, Apr. 13, 2018.
- Luke, M. *Biomaterials as Pertains to Drug Products, Including Generic Drug Products with Biomaterial Components*. Presentation at BEMA Summer 2018 Meeting. Woods Hole, MA, June 28, 2018.
- Jiang, W. *Regulatory Research in Nanomedicine Drug Products*. Presentation at AAPS Annual Guidance Forum. Rockville, MD, Sept. 11, 2018.
- 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.
- 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.
- Tyner, Katherine. *Trends and Regulatory Considerations for Drug Products Containing Nanomaterials,* Presentation at NCI Alliance for Nanotechnology in Cancer PI Meeting. Rockville, MD, 10/10 2018.

- Tyner, Katherine. *Trends and Regulatory Considerations for Drug Products Containing Nanomaterials: CDER Perspective.* Presentation at Indo-US Nanosafety Evaluation Workshop. New Delhi, India, 10/23, 2018.
- Tyner, Katherine. *Regulatory Considerations for Drug Products Containing Nanomaterials: CDER Perspective.* Presentation at Indo-US Nanosafety Evaluation Workshop. New Delhi, India, 10/23, 2018.
- Tyner, Katherine. *Regulatory Considerations for Drug Products Containing Nanomaterials: US FDA Perspective.* Presentation at Indo-US Bilateral Symposium on Nanotechnology and Regulatory Science. Hyderabad, India, 02/21, 2018.
- Tyner, Katherine. *International Standards Organization TC 229*, 2018, Invited presentation, Standards Readiness for Liposome Drug Products. *Webex,* 5/7/2018
- Tyner, Katherine. JRC/NIST Nanotechnology Workshop, Ispra, Italy, 12/04/2018, Invited Presentation, Regulatory Perspectives and Standards Priorities for Products Containing Nanomaterials: US FDA
- Tyner, Katherine. *AAPS Guidance Forum*, 2019, invited presentation, Regulatory Considerations for Drug Products Containing Nanomaterials: US FDA Perspective. Silver Spring, MD, Sept. 11, 2018.
- Tyner, Katherine. *Emerging Regulatory Guidance for Drug Products Containing Nanomaterials: US-FDA Perspective*. CLINAM, Basel, Switzerland. September 3, 2018
- Tyner, Katherine. *Regulatory Considerations for Drug Products Containing Nanomaterials: US-FDA Perspective*. CLINAM, Basel, Switzerland. September 3, 2018

Posters

- Ansar, SM., Jiang, W., and Mudalige, T. *Simultaneous Separation and Quantification of Free Drug and Liposome-Associated Drug by Capillary Electrophoresis with UV-Vis detection*. Poster Presentation at 2017 American Chemical Society Annual Meeting. Washington DC, August 20, 2017.
- Koo, B. *Scientific Considerations for an In Vitro Bioequivalence Approach for Ultrasound Contrast Agent Products: Characterizing How Size Distribution and Concentration Affect Echogenicity*. Poster Presentation at Generic Drug Science Day. Silver Spring, MD, Nov. 28, 2017.
- Manna, S. *Assessing In Vitro Drug Release from Multivesicular Liposome: Comparison of Reverse Dialysis and Rotary Shaking Methods*. Poster Presentation at Generic Drug Science Day. Silver Spring, MD, Nov. 28, 2017.
- Myung, JH., Zheng, J., and Kozak, D. *Comparative Validation of Single Nanoparticle Counting Techniques for Regulatory Review of Complex Drug Products Containing Nanomaterials.* Poster Presentation at Generic Drug Science Day. Silver Spring, MD, Nov. 28, 2017.
- Myung, JH. *Assessing Particle Counting Techniques to Improve the Regulatory Review of Complex Colloidal Drug Products*. Poster Presentation at ACS Colloids and Surface Science Symposium. New York, NY, July 7, 2017.
- Myung, J., Kozak, D., and Zheng, J. *Assessing High-Resolution Nanoparticle Counting Techniques for the Regulatory Science of Complex Drug Products*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.
- Myung, J., Zheng, J., and Kozak, D. *Assessing High-Resolution Single Nanoparticle Counting Techniques to Improve the Regulatory Science of Complex Drug Products*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Petrochenko, P. *Comparative Evaluation of Particle Sizing Techniques for Measuring the Globule Size Distributions of Cyclosporine Ophthalmic Emulsions*. Poster Presentation at Generic Drug Science Day. Silver Spring, Nov. 28, 2017.

- Petrochenko, P., Wong, S., Wu, Y., Zheng, J., Xu, X., Choi, S., and Kozak, D. *Continuous Monitoring of Albumin-Bound Paclitaxel Dissolution Profiles Using Dynamic Light Scattering and in Situ UV/Vis Fiber-Optic Probes*. 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.
- Stern, S., Skoczen, S., Snapp, K., Crist, R., and McNeil, S. *Novel Method to Determine Bioequivalence of Complex Drugs*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.
- 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.
- Wu, Y., Petrochenko, P., Koo, B., Manna, S., Myung, JH., Choi, S., Kozak, D., and Zheng, J. *Distinguish Coexistence of Nanoemulsion and Liposome in Propofol by Cryogenic Transmission Electron Microscopy*. Poster Presentation at Microscopy and Microanalysis Annual Meeting. St. Louis, MO, August 6, 2017.
- Wu, Y., Petrochenko, P., Liu, J., Manna, S., Koo, B., Myung, J.H., Chen, L., Choi, S., Kozak, D., and Zheng, J. *Evaluating Complex Emulsion and Liposome Morphology in Propofol Drug Products with High Resolution Cryogenic Electron Microscopy*. Poster Presentation at AAPS 2017 Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Wu, Y. *Revealing Complex Morphology in Propofol Drug Products using Cryogenic Transmission Electron Microscopy (Cryo-TEM).* Poster Presentation at Generic Drug Science Day. Silver Spring, MD, Nov. 28, 2017.
- Wu, Y., Petrochenko, P., Liu, J., Manna, S., Koo, B., Myung, J., Chen, L., Choi, S., Kozak, D., and Zheng, J. *Evaluating Complex Emulsion and Liposome Morphology in Propofol Drug Products with High Resolution Cryogenic Electron Microscopy*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Yong, W., Peter, P., Bonhye, K., Soumyarwit, M., Ja, H. M., Stephanie, C., Darby, K., and Jiwen, Z. *Revealing Complex Morphology in Propofol Drug Products Using Cryogenic Transmission Electron Microscopy (Cryo-TEM)*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.