CDER Critical Path Projects: Sample Publications

Title	Examples of Publications*
Development of methods for analysis of biologic drugs: Molecular fingerprinting by MS and NMR	1) Hadwiger ME, Sommers CD, Mans DJ, Patel V, Boyne MT 2nd. Quality assessment of U.S. marketplace vancomycin for injection products using high-resolution liquid chromatography-mass spectrometry and potency assays. Antimicrob Agents Chemother.2012 Jun;56(6):2824-30. 2) Aubin, Y., Freedberg, D.I. and Keire, D.A., (2014) "One- and two-dimensional NMR techniques" in Biophysical Characterization of Proteins in Developing Biopharmaceuticals, Eds. Houde. D.J. and Berkowitz, S.A., Elsevier, In Press
Development of process analytical technology (PAT) tools for automated sampling and analysis of mammalian cell culture	1) Read EK, Shah RB, Riley BS, Park JT, Brorson KA, Rathore AS. Process analytical technology (PAT) for biopharmaceutical products: Part II. Concepts and applications. Biotechnol Bioeng. 2010 Feb 1;105(2):285-95. 2) Gottschalk U, Brorson K, Shukla AA. The need for innovation in biomanufacturing. Nat Biotechnol. 2012 Jun 7;30(6):489-92.
Root cause analysis for drug product recalls	1) Torbeck LD, Friedman RL, Smedley M. An overview of the CDER drug recall root cause research project. Pharmaceutial Technology Volumn 33, Issue 8, pp. 42-45 2) Friedman RL, Smedley M, Torbeck LD, Santiago I. An initial report of CDER's recall root cause research project (part II). Pharmaceutical Technology, Volume 35, Issues
Application of model-based quantitative methods for drug regulatory risk-benefit assessment - A search for a reproducible and systematic approach	1) Crentsil V, Lee J, Jackson A. Quantitative drug benefit-risk assessment: utility of modeling and simulation to optimize drug safety in older adults. Ann Pharmacother. 2014 Mar;48(3):306-13. doi: 10.1177/1060028013514376. Epub 2014 Jan 28. PubMed PMID: 24473487.
A public health model for optimal use of antihypertensive therapy	1) Jin Y, Bies R, Gastonguay MR, Stockbridge N, Gobburu J, Madabushi R. Misclassification and discordance of measured blood pressure from patient's true blood pressure in current clinical practice: a clinical trial simulation case study. J Pharmacokinet Pharmacodyn. 2012 Jun;39(3):283-94. 2) Jin Y, Bies R, Gastonguay MR, Wang Y, Stockbridge N, Gobburu J, Madabushi R. Predicted impact of various clinical practice strategies on cardiovascular risk for the treatment of hypertension: a clinical trial simulation study. J Pharmacokinet Pharmacodyn. 2014 Dec;41(6):693-704.
Advanced methods for in vitro testing of inhalation products	1) Liu X, Doub WH, Guo C. Assessment of the influence factors on nasal spray droplet velocity using phase-Doppler anemometry (PDA). AAPS PharmSciTech. 2011 Mar;12(1):337-43. 2) Liu X, Doub WH, Guo C. Evaluation of droplet velocity and size from nasal spray devices using phase Doppler anemometry (PDA). Int J Pharm. 2010 Mar 30;388(1-2):82-7.
Workshop: Membrane transporters in drug development	1) Huang SM, Zhang L, Giacomini KM. The International Transporter Consortium: a collaborative group of scientists from academia, industry, and the FDA. Clin Pharmacol Ther. 2010 Jan;87(1):32-6.(Transporter workshop proceedings) 2) The International Transporter Consortium, KM Giacomini, S-M Huang, DJ Tweedie, LZ Benet, KLR Brouwer, X Chu, A Dahli, R Evers, V Fischer, KM Hillgren, KA Hoffmaster, T Ishikawa, D Keppler, RB Kim, CA Lee, M Niemi, JW Polli, Y Sugiyama, PW Swaan, JA Ware, SH Wright, SW Yee, MJ Zamek-Gliszczynski, and L Zhang. Membrane Transporters in Drug Development. Nat.Rev Drug Discov. 9 (3):215-236, 2010. (Transporter whitepaper)
Development of a membrane transporter database	1) Morrissey KM, Wen CC, Johns SJ, Zhang L, Huang SM, Giacomini KM. The UCSF-FDA TransPortal: a public drug transporter database. Clin Pharmacol Ther. 2012 Nov;92(5):545-6.
Antiviral Information Management System (AIMS) to improve clinical trial design and analysis	1) Chen J, Florian J, Carter W, Fleischer RD, Hammerstrom TS, Jadhav PR, Zeng W, Murray J, Birnkrant D. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. Gastroenterology. 2013 Jun;144(7):1450-1455. 2) Jadhav PR, Neal L, Florian J, Chen Y, Naeger L, Robertson S, Soon G, Birnkrant D. Antiviral Information Management System (AIMS): a prototype for operational innovation in drug development. J Clin Pharmacol. 2010 Sep;50(9 Suppl):50S-55S.
Development of Improved Strategies for Biotechnology Product Physicochemical Comparability and Biosimilarity Assessments	1) Bones J, Mittermayr S, McLoughlin N, Hilliard M, Wynne K, Johnson GR, Grubb JH, Sly WS, Rudd PM. Identification of N-Glycans Displaying Mannose-6-Phosphate and their Site of Attachment on Therapeutic Enzymes for Lysosomal Storage Disorder Treatment. Analytical Chemistry 2011; 83(13): 5344-5352. 2) Madhavarao CN, Agarabi CD, Wong L, Müller-Loennies S, Braulke T, Khan M, Anderson H, Johnson GR. Evaluation of butyrate-induced production of a mannose-6-phosphorylated therapeutic enzyme using parallel bioreactors. Biotechnology and Applied Biochemistry. Article first published online: 20 FEB 2014; DOI: 10.1002/bab.1151
Comparative studies of therapeutic protein secondary structure using deep ultraviolet resonance raman spectroscopy	1) Arzhantsev S, Vilker V, and Kauffman J. Deep UV Resonance Raman Spectroscopy as a Tool for Quality Control of Formulated Therapeutic Proteins, Applied Spectroscopy (2012) 66, 1262-1268
Standardization of spectral libraries for rapid screening of pharmaceuticals	1) Kauffman JF, Rodriguez JD, Gryniewicz-Ruzicka CM, Arzhantsev S, D'Sa A, Uratani B, Wolfgang S, Westenberger BJ, Buhse, LF, Dunn, JD, Mecker-Pogue, LC. Securing the supply chain through Rapid Screening of pharmaceutical materials. BioPharma Asia. (2013) 16, 28-37. 2) Kauffman JF, Arzhantsev S, Saettele AL, Berry KA, Benjamin J. Westenberger, and Buhse LF. Transferring Raman Spectral Libraries and Chemometric-Based Methods Between Different Instruments and Platforms, American Pharmaceutical Review, (2013) 16, 9-18.
Metal impurities in pharmaceuticals	1) Gang Li and John Kauffman,"A survey of elemental impurities in pharmaceutical excipients" (pending) 2) Gang Li and John Kauffman, "Elemental impurities in drug products: as survey" (pending) 3) Ganl Li, Olen Stephens and John Kauffman, "Elemental impurities in small volume parenterals" (pending)

Title	Examples of Publications*
Linking marketplace heparin product attributes and manufacturing processes to bioactivity and immunogenicity	1) Keire DA, Trehy ML, Reepmeyer JC, Kolinski RE, Dunn J, Ye W, Westenberger BJ, and Buhse LF. Analysis of crude heparin by 1H-NMR, capillary electrophoresis, and strong-anion-exchange-HPLC for contamination by over sulfated chondroitin sulfate. J. Pharm. Biomed. Anal. 2010; 51(4), 921-926. 2) Zang Q, Keire DA, Wood RD, Buhse LF, Moore CMV, Nasr M, al-Hakim A, Trehy ML and Welsh WJ, Combining 1H NMR Spectroscopy and Chemometrics to Identify Heparin Samples that May Possess Dermatan Sulfate (DS) Impurities or Oversulfated Chondroitin Sulfate (OSCS) Contaminants. J. Pharm. Biomed. Anal. 2011; 54(5), 1020-1029.
Pharmaceutical and bioequivalence evaluation of several generic and brand products	1) Woodcock J, Khan M, Yu LX. Withdrawal of generic budeprion for nonbioequivalence. N Engl J Med. 2012 Dec 27;367(26):2463-5. N Engl J Med. 2012 Dec 27;367(26):2463-5. 2) Zhao N, Zidan A, Tawakkul M, Sayeed VA, Khan MA. Tablet splitting: Product quality assessment of metoprolol succinate extended release tablets. Int J Pharm, 2010, 401:25-31.
Liposomal protein drug products: A quality by design case study to understand and manage the risks with product and process variabilities	1) Xu X, Costa A, Khan MA, and Burgess DJ. Application of quality by design to formulation and processing of protein liposomes. International Journal of Pharmaceutics. 2012; 434(1-2): pp. 349-359. 2) Xu X, Costa A, and Burgess DJ. Protein encapsulation in unilamellar liposomes: high encapsulation efficiency and a novel technique to assess lipid-protein interaction. Pharmaceutical Research 2012; 29: pp. 1919-1931.
A complement related biomarker for acute inflammatory drug reactions	1) Zhou ZH, Chen T, Arora K, Hyams K, Kozlowski S. Complement C1 esterase inhibitor levels linked to infections and contaminated heparin-associated adverse events. PLoS One. 2012;7(4):e34978. 2) Zhou ZH, Rajabi M, Chen T, Karnaukhova E, Kozlowski S. Oversulfated chondroitin sulfate inhibits the complement classical pathway by potentiating C1 inhibitor. PLoS One. 2012;7(10):e47296.
Knowledge management tool for creating cross-disciplinary multiple-NDA disease database	1) Jadhav PR, Neal L, Florian J, Chen Y, Naeger L, Robertson S, Soon G, Birnkrant D. Antiviral Information Management System (AIMS): a prototype for operational innovation in drug development. J Clin Pharmacol. 2010 Sep;50(9 Suppl):50S-55S. 2) Hemodynamic Determinants of Exercise Capacity in PAH. Brar S. Reports to EMEA Regulatory agency (the European equivalent of the FDA), Mar. 2010 3) Hemodynamic determinants of Exercise Capacity in Idiopathic Pulmonary Arterial Hypertension. Brar S. to be submitted to American Journal of Respiratory and Critical Care Medicine in Oct 2010.
Evaluating the effects of formulation and device changes on in vitro performance for dry powder inhalers	1) Shur J, Lee S, Adams W, Lionberger R, Tibbatts J, Price R. Effect of device design on the in vitro performance and comparability for capsule-based dry powder inhalers. AAPS J 2012 Dec;14(4):667-76 2)Adams WP, Lee SL, Plourde R, Lionberger RA, Bertha CM, Doub WH, Bovet JM, Hickey AJ. Effects of device and formulation on in vitro performance of dry powder inhalers. AAPS J 2012 Sep;14(3):400-9
Quality by design for orally inhaled drug products: Chemistry, manufacturing, and controls	1) Depasquale R, Lee SL, Saluja B, Shur J, Price R. The Influence of Secondary Processing on the Structural Relaxation Dynamics of Fluticasone Propionate. AAPS PharmSciTech. 2014 Nov 15.
Systems biology approach for predicting complex drug interactions: Building model with omeprazole as a perpetrator drug	1) Wu F, Gaohua L, Zhao P, Jamei M, Huang SM, Bashaw ED, Lee SC. Predicting nonlinear pharmacokinetics of omeprazole enantiomers and racemic drug using physiologically based pharmacokinetic modeling and simulation: application to predict drug/genetic interactions. Pharm Res. 2014 Aug;31(8):1919-29.
Computational modeling of bioavailability and bioequivalence	1) Jiang W, Kim S, Zhang X, Lionberger RA, Davit BM, Conner DP, Yu LX. The role of predictive biopharmaceutical modeling and simulation in drug development and regulatory evaluation Int J Pharm. 2011 Oct 14;418(2):151-60. Epub 2011 Jul 23. 2) Yu L, Zhang X, Lionberger R. Modeling and mechanistic approaches for oral absorption: quality by design in action. Ther Deliv. 2012 Feb;3(2):147-50.
Syngeneic animal model for studying the cardiac safety and efficacy of oncology agents	1) Dickey JS, Gonazalez Y, Aryal B, Mog S, Nakamura A, Redon C, Baxa U, Rosen E, Cheng G, Zielonka J, Parekh P, Mason K, Joseph J, Kalyanaraman B, Bonner W, Herman E, Shacter E, and Rao VA. Mito-tempol and dexrazoxane exhibit cardioprotective and chemotherapeutic effects through specific protein oxidation and autophagy in a syngeneic breast tumor preclinical model. PLOS One 2013 Aug 5;8(8):e70575.
Protein biomarkers for testing the potential clinical utility of novel chemoprotective drugs	1) Rao VA, Klein SR, Bonar SJ, Zielonka J, Mizuno N, Dickey JS, Keller PW, Joseph J, Kalyanaraman B, Shacter E. The antioxidant transcription factor Nrf2 negatively regulates autophagy and growth arrest induced by the anticancer redox agent mitoquinine. J Biol Chem 2010;285(45): 34447-59.
SmartTots (Strategies for mitigating anesthesia related neurotoxicity it tots) Public private partnership (PPP) under PASI (pediatric anesthesia safety initiative)	1) Rappaport B, Mellon RD, Simone A, Woodcock J. Defining safe use of anesthesia in children. N Engl J Med. 2011 Apr 14;364(15):1387-90. 2) Ing C, DiMaggio C, Whitehouse A, Hegarty MK, Brady J, von Ungern-Sternberg BS, Davidson A, Wood AJ, Li G, Sun LS. Long-term differences in language and cognitive function after childhood exposure to anesthesia. Pediatrics. 2012 Sep;130(3):e476-85.
Analgesic clinical trials project (ACTP)	1) Rappaport B, Cerny I, and Sanhai W. ACTION on the Prevention of Chronic Pain after Surgery. Anesthesiology 112 2010; 509-10. 2) Dworkin RH, Turk DC, Peirce-Sandner S, McDermott MP, Farrar JT, Hertz S, Katz NP, Raja SN, Rappaport BA. Placebo and treatment group responses in postherpetic neuralgia vs. painful diabetic peripheral neuropathy clinical trials in the REPORT database. Pain 2010;150:12-16.
The analgesic, anesthetic, and addiction clinical trial translation, innovations, opportunities and networks (ACTION)	1) Dworkin RH, Turk DC. Accelerating the development of improved analgesic treatments: the ACTION public-private partnership. Pain Medicine, 2011;12:S109-S117. 2) McDermott MP, Rappaport BA, Sanhai WR. Evidence-based clinical trial design for chronic pain pharmacotherapy: a blueprint for ACTION. Pain 2011b;152(suppl):S107-S115.

Title	Examples of Publications*
Should inclusion of obese patients be a requirement when considering clinical trials for the purpose of registration?	1) Jain R, Chung S , Jain L, Khurana M, Lau SWJ, Lee JE, Vaidyanathan J, Zadezensky I, Choe S, and Sahajwalla CG. Implications of Obesity on Drug Therapy: Limitations and Challenges. Clinical Pharmacology and Therapeutics, 2011 July; 90(1), 77-89 2) Jain R, Liu D, Chung S , Khurana M, Vaidyanathan J, Zadezensky I, and. Sahajwalla CG. Predictive Drug Clearance in Obese Subjects: Analysis by PBPK and Allometric Scaling. (In Preparation)
Co-sponsored workshop with NYAS on therapeutic proteins	1)"Pharmacologic Administration of Interleukin-2: Inducing a Systemic Autophagic Syndrome?" (pages 14 -27) Antonio Romo de Vivar Chavez, William Buchser, Per H. Basse, Xiaoyan Liang, Leonard J. Appleman, Jodi K. Maranchie, Herbert Zeh, Michael E. de Vera and Michael T. Lotze
Cell culture and animals models for evaluation of drug-induced pancreatitis and ductal metaplasia	1) Rouse R, Xu L, Stewart S, Zhang L, Zhang J. 2014. GLP-1 signaling drug induced injury of the exocrine pancreas in mice is exacerbated by high fat diet. Toxicology and Applied Pharmacology (accepted 2-Feb 2014). 2) Rouse R, Rosenzweig B, Thompson K. 2013. Circulating microRNAs as biomarkers of drug-induced pancreatitis. microRNAs in Toxicology and Medicine. Saura Sahu, editor. John Wiley & Sons, Ltd.
Improving the physical and toxicological characterization of nanoparticle therapeutic pharmaceuticals	1) Keene AM, Allaway RJ, Sadrieh N, Tyner KM. Gold nanoparticle trafficking of typically excluded compounds across the cell membrane in JB6 Cl 41-5a cells causes assay interference. Nanotoxicology. 2011 Dec;5(4):469-78.
Product quality issues with tablet splitting	1) Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation - published March 2013 2) Shah RB, Collier JS, Sayeed VA, Bryant A, Habib MJ, Khan MA. Tablet splitting of a narrow therapeutic index drug: a case with levothyroxine sodium. AAPS PharmSciTech. 2010 Sep;11(3):1359-67.
Development of in vitro predictive methods and necessary data analyses tools for dissolution/release specification setting and for ensuring intended product performance in the target patient population	1) Nielsen LH, Gordon S, Holm R, Selen A, Rades T, Müllertz A. Preparation of an amorphous sodium furosemide salt improves solubility and dissolution rate and leads to a faster Tmax after oral dosing to rats. Eur J Pharm Biopharm. 2013 Nov;85(3 Pt B):942-51. 2) Gordon S, Naelapää K, Rantanen J, Selen A, Müllertz A, Østergaard J. Real-time dissolution behavior of furosemide in biorelevant media as determined by UV imaging. Pharm Dev Technol. 2013 Nov-Dec;18(6):1407-16.
Safety analysis in HIV trials	1) Soon GG, Min M, Struble KA, Chan-Tack KM, Hammerstrom T, Qi K, Zhou S, Bhore R, Murray JS, Birnkrant DB. Meta-analysis of gender differences in efficacy outcomes for HIV-positive subjects in randomized controlled clinical trials of antiretroviral therapy (2000-2008). AIDS Patient Care STDS. 2012 Aug;26(8):444-53. 2) Smith F, Hammerstrom T, Soon G, Zhou S, Chen BB, Mai YB, Struble K, Huque M. A Meta-analysis to Assess the FDA DAVP's TLOVR Algorithm in HIV Submissions.Drug Info J 2011 May;45(3):291-300
Streamlining clinical trials for accessing new drugs potential to delay cardiac repolarization	1) Garnett CE, Zhu H, Malik M, Fossa AA, Zhang J, Badilini F, Li J, Darpö B, Sager P, Rodriguez I. Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic effects. Am Heart J. 2012 Jun;163(6):912-30. 2) Florian J, Garnett CE, Nallani SC, Rappaport BA, Throckmorton DC. A modeling and simulation approach to characterize methadone QT prolongation using pooled data from five clinical trials in MMT patients. Clin Pharmacol Ther. 2012 Apr;91(4):666-72.
Application of -omic technology to the evaluation of the toxicological significance of drug induced phospholipidosis (DIPL)	1) Thompson KL, Haskins K, Rosenzweig BA, Stewart S, Zhang J, Peters D, Knapton A, Rouse R, Mans D, Colatsky T. Comparison of the diagnostic accuracy of di-22:6-bis(monoacylglycerol)phosphate and other urinary phospholipids for drug-induced phospholipidosis or tissue injury in the rat. Int J Toxicol, 31(1), 14-24, 2012. 2) Thompson KL, Zhang J, Stewart S, Rosenzweig BA, Shea K, Mans D, Colatsky T. Comparison of urinary and serum levels of di-22:6-bis(monoacylglycerol)phosphate as noninvasive biomarkers of phospholipidosis in rats. Toxicol Lett, 213, 285-291, 2012.
Determining the effect of delivery medium on the biodistribution of nanoparticles in in vivo and in vitro models	1) Keene AM, Peters D, Rouse R, Stewart S, Rosen ET, Tyner KM. Tissue and cellular distribution of gold nanoparticles varies based on aggregation/agglomeration status. Nanomedicine. 2012;7(2) 199-209. 2) Keene, A.M, Tyner, K.M. Analytical Characterization of Gold Nanoparticle Primary Particles, Aggregates, Agglomerates and Agglomerated Aggregates. Journal of Nanoparticle Research. 2011;13 3465-81.
Nanoparticle toxicity predictions using an in vitro systems- biology approach	1)Bancos S, Tsai DH, Hackley VA, Weaver J, Tyner KM. Evaluation of viability and proliferation profiles on macrophages treated with silica nanoparticles in vitro via plate-based, flow cytometry, and Coulter counter assays. ISRN Nanotechnology. 454072, doi:10.5402/2012/454072 (2012). 2) Keene, A.M., Bancos, S., Tyner, K.M. "Considerations for in vitro nanotoxicity testing" in Handbook of Nanotoxicology and Nanomedicine, Saura Sahu, Daniel Casciano, eds. John Wiley and Sons. 2014 anticipated publication date
Optimization of drug development in pediatric type 2 diabetes	1) Type 2 diabetes in pediatrics and adults: Thoughts from a clinical pharmacology perspective. J Vaidyanathan, S Choe, C Sahajwalla. Vol 101 (5), 1659-1671 (2012). Journal of Pharmaceutical Sciences.
Building an in silico tool for screening new drugs for QT prolongation potential using human clinical trial data	1) Valerio LG Jr, Balakrishnan S, Fiszman ML, Kozeli D, Li M, Moghaddam S,Sadrieh N. Development of cardiac safety translational tools for QT prolongation and torsade de pointes. Expert Opin Drug Metab Toxicol. 2013 Jul;9(7):801-15. 2) Valerio LG Jr. In silico toxicology models and databases as FDA Critical Path Initiative toolkits. Hum Genomics. 2011 Mar;5(3):200-7. Review
Development and evaluation of an assay to assess early indicators of innate immune activation and inflammation in peripheral blood and tissues of non-human primates	1) CpG ODN and Imiquimod induce distinct type I IFN responses in humans and non-human primates. Montserrat Puig, Kevin W. Tosh, Lucja Grajkowska, Kevin Kirschman, Cecilia Tami, Lynsie Schramm, Ronald Rabin, Daniela Verthelyi. In preparation.

Title	Examples of Publications*
Impact of kidney disease on drug metabolism	1) Volpe DA, Tobin GA, Tavakkoli F, Dowling TC, Parker RJ. Effect of uremic serum and uremic toxin on in vitro microsomal metabolism. Drug Metab Rev. 2012; 44(S1):57-58. 2) Volpe DA, Tobin GA, Tavakkoli F, Dowling TC, Light PD, Parker RJ. Effect of uremic serum and uremic toxin on drug metabolism in human microsomes. Reg Toxicol Pharmacol. 2103 [http://dx.doi.org/10.1016/j.yrtph.2013.10.006] (article in press)
Rapid screening of pharmaceutical products and ingredients	1) John F. Kauffman, Connie M. Gryniewicz-Ruzicka, Sergey Arzhantsev, Jamie D. Dunn, John A. Spencer, Steven Wolfgang, Xiang Li, Lindsey N. Pelster, Benjamin J. Westenberger and Lucinda F. Buhse, Pharmaceutical Surveillance with Rapid Spectroscopic Screening Technologies, American Pharmaceutical Review (2010) 13 (1) 58-64 2) Connie M. Gryniewicz-Ruzicka, Sergey Arzhantsev, Lindsey N. Pelster, Benjamin J. Westenberger, Lucinda F. Buhse, and John F. Kauffman, Multivariate Calibration Standardization Transfer Across Multiple Instruments for the Rapid Detection of Diethylene Glycol in Glycerin by Raman Spectroscopy, Applied Spectroscopy (2011) 65, 334-341
Investigating the molecular mechanism contributing to Herceptin (trastuzumab) resistance of human breast cancer	1) Dokmanovic M, Hirsch DS, Shen Y, Wu WJ. (2009) Rac1 contributes to trastuzumab resistance of breast cancer cells: Rac1 as a potential therapeutic target for the treatment of trastuzumab-resistant breast cancer. Mol Cancer Ther. 8:1557-69. 2) Dokmanovic M, Hirsch DS, Shen Y, Bonacci TM, Wu WJ. (2011) Trastuzumab regulates IGFBP-2 and IGFBP-3 to mediate growth inhibition: implications for the development of predictive biomarkers for trastuzumab-resistance. Molecular Cancer Therapeutics. In press.
Investigation of new therapeutic targets and development of novel therapeutic approaches and predictive biomarkers for trastuzumab resistant breast cancers	1) ElZarrad MK, Mukhopadhyay P, Mohan N, Hao E, Dokmanovic M, Hirsch DS, Shen Y, Pacher P, Wu WJ. Trastuzumab alters the expression of genes essential for cardiac function and induces ultrastructural changes of cardiomyocytes in mice. PLoS ONE 2013;8(11): e79543. doi:10.1371/journal.pone.0079543. 2) Dokmanovic M, ElZarrad MK, Hirsch DS and Wu WJ. Antibody-drug conjugates as therapeutic agents in oncology: overview and perspectives. Bentham eBook. 2013:2:139-189. (ISBN: 978-1-60805-808-2 ISBN: 978-1-60805-809-9 ISSN :1879-6656).
Application of renal function biomarkers for dose adjustment - A systematic evaluation of safety and efficacy	1) Zhang L, Xu N, Xiao S, Arya V, Zhao P, Lesko LJ, and S-M Huang. Regulatory Perspectives on Designing Pharmacokinetic Studies and Optimizing Labeling Recommendations for Patients with Impaired Kidney Function. Journal of Clinical Pharmacology. 2012 Jan; 52 (1 Suppl):79S-90S. 2) Park EJ, Pai MP, Dong T, Zhang J, Ko CW, Lawrence J, Crentsil V, Zhang L, Xu NN. The influence of body size descriptors on the estimation of kidney function in normal weight, overweight, obese, and morbidly obese adults. Ann Pharmacother. 2012 Mar;46(3):317-28.
Detection of alternate glycoforms derived from various recombinant processes	1) Ye H, Boyne MT 2nd, Buhse LF, Hill J. Direct approach for qualitative and quantitative characterization of glycoproteins using tandem mass tags and an LTQ Orbitrap XL electron transfer dissociation hybrid mass spectrometer. Anal Chem.2013 Feb 5;85(3):1531-9. 2) Ye H, Hill J, Gucinski AC, Boyne MT 2nd, Buhse LF. Direct Site-Specific Glycoform Identification and Quantitative Comparison of Glycoprotein Therapeutics: Imiglucerase and Velaglucerase Alfa. AAPS J. 2014 Dec 13. [Epub ahead of print] PubMed PMID: 25501675.
Characterization of circulating tumor cells in blood as biomarker for cancer metastasis	1) Chen JJ, Shen HC, Rivera Rosado LA, Zhang Y, Di X, Zhang B. Mislocalization of death receptors correlates with cellular resistance to their cognate ligands in human breast cancer cells. Oncotarget. 2012 Aug;3(8):833-42. 2) Di X, Zhang G, Zhang Y, Takeda K, Rivera Rosado LA, Zhang B. Accumulation of autophagosomes in breast cancer cells induces TRAIL resistance through downregulation of surface expression of death receptors 4 and 5. Oncotarget. 2013 Sep;4(9):1349-64.
Biomarkers for prediction of tumor responsiveness to death receptor-targeting therapies	1) Yoshida T, Zhang Y, Rivera Rosado LA, Chen J, Khan T, Moon SY, Zhang B. Blockade of Rac1 activity induces G1 cell cycle arrest or apoptosis in breast cancer cells through downregulation of cyclin D1, survivin, and X-linked inhibitor of apoptosis protein. Mol Cancer Ther. 2010 Jun;9(6):1657-68. 2) Zhang Y, Yoshida T, Zhang B. TRAIL induces endocytosis of its death receptors in MDA-MB-231 breast cancer cells. Cancer Biol Ther. 2009 May;8(10):917-22.
Development of an apoptosis assay for evaluation of cancer therapeutics	1) Zhang Y, Rivera Rosado LA, Moon SY, Zhang B. Silencing of D4-GDI inhibits growth and invasive behavior in MDA-MB-231 cells by activation of Rac-dependent p38 and JNK signaling. J Biol Chem. 2009 May 8;284(19):12956-65. 2) Brunelle JK, Zhang B. Apoptosis assays for quantifying the bioactivity of anticancer drug products. Drug Resist Updat. 2010 Dec;13(6):172-9.
Investigation of the relative contribution of phase II drug metabolizing enzymes to aceteaminophen clearance and their implications to the acetaminophen induced liver toxicity in humans with the aid of physiologically based pharmacokinetic (PBPK) modeling	1) Jiang XL, Zhao P, Barrett JS, Lesko LJ, Schmidt S. Application of physiologically based pharmacokinetic modeling to predict acetaminophen metabolism and pharmacokinetics in children. CPT Pharmacometrics Syst Pharmacol. 2013 Oct 16;2:e80.
Development of the FDA drug-drug interaction database	1) Vieira MD, Kim MJ, Apparaju S, Sinha V, Zineh I, Huang SM, Zhao P. PBPK model describes the effects of comedication and genetic polymorphism on systemic exposure of drugs that undergo multiple clearance pathways. Clin Pharmacol Ther. 2014 May;95(5):550-7. 2) Wu F, Gaohua L, Zhao P, Jamei M, Huang SM, Bashaw ED, Lee SC. Predicting nonlinear pharmacokinetics of omeprazole enantiomers and racemic drug using physiologically based pharmacokinetic modeling and simulation: application to predict drug/genetic interactions. Pharm Res. 2014 Aug;31(8):1919-29.

*Illustrative examples of publications resulting from CDER Critical Path (CP) Projects.