FY2018 GDUFA Science and Research Report: Complex Mixtures and Peptides

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: Complex Mixtures and Peptides (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm549165.htm)
- FYs 2013-2017 GDUFA Science and Research Report: Complex Mixtures and Peptides (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm604321.htm)

Introduction

The focus of FDA's research effort has been on the continued development of sensitive analytical tools and methods for characterizing complex active pharmaceutical ingredients (APIs) and related impurities in complex mixtures and peptides. This effort led to the publication of a draft guidance on synthetic peptides that refer to listed drugs (i.e., Reference Listed Drugs (RLDs)) of recombinant deoxyribonucleic acid (rDNA) origin. This guidance discusses when an application for a synthetic peptide drug product (synthetic peptide) that refers to a previously approved peptide drug product of rDNA origin (peptide of rDNA origin) should be submitted as an abbreviated new drug application (ANDA) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) rather than as a new drug application (NDA). While the guidance discusses when submission of an ANDA may be appropriate for certain peptide drug products, FDA recognizes there are still many challenges in the compositional analysis and characterization of the complex APIs, including impurity profile analysis in peptides and synthetic oligonucleotides, and assessment of the associated safety risk like immunogenicity.

In FY18, we continued to investigate complex API mixture characterization through an external research project on profiling pentosan polysulfate sodium (PPS) and its metabolites in patient urine with mass spectrometry (MS). The aim of this project was to identify key fragments or metabolites peaks with sensitive MS methods to characterize the PPS mixture. In the area of developing more sensitive analytical methods, we are working to improve the existing analytical method recommended in the product-specific guidance on conjugated estrogens tablet. The goal is to have a high resolution ultra-high performance liquid chromatography (UHPLC)-MS/MS method which can be used to identify and characterize both the steroidal and non-steroidal components presented in the conjugated estrogens tablet.

We have initiated several internal research projects with the focus of identifying and characterizing various impurities in peptide products, including host cell proteins (HCPs) in peptides of rDNA origin, D-isomers in synthetic L-amino acid peptides, and peptide-related impurity profiles of teriparatide. For example, we have developed a MS-based method to detect and quantify two HCPs in FORTEO® (teriparatide of rDNA origin) (**Table 1 and Figures 1 and 2**).

Another area of research interest is the characterization of synthetic oligonucleotides and their impurity profile. Synthetic oligonucleotides have attracted broad attention because of the wide range of potential therapeutic effects this class of drugs can bring. Due to their structural and compositional complexity as a mixture of numerous diastereomers and their structurally-similar impurities, characterization of the synthetic oligonucleotides and those related impurities is very challenging.

The fourth area of interest is the characterization of synthetic polymers. One example is the collaboration between FDA and the National Institute for Pharmaceutical Technology and Education (NIPTE) on the characterization of patiromer, a synthetic polymeric drug used for hyperkalemia, with solid state ^{13}C NMR technology.

We are also initiating projects both internally and externally to develop new in silico and in vitro methods to evaluate the potential immunogenicity risk of impurities in peptide products. While some research was undertaken to assess the immunogenicity potential of peptide-related impurities during GDUFA I, new methods are still needed to improve the correlation of results from in vitro models to human clinical findings. In addition, we have initiated projects to study and develop methods for measuring the immunogenicity of synthetic oligonucleotides. Measuring immunogenicity is challenging because there is very limited data in this area and it is difficult to separate impurities.

These research activities will help address unmet regulatory needs in terms of complex API characterization and development of API sameness standards for drugs with complex mixtures as the drug substance. Results from these studies will inform the development of product-specific guidance and, thus, facilitate the development of generic versions of these complex drugs which would otherwise be challenging. We will continue to strengthen and broaden the research in this area to address other scientific and regulatory challenges in the development of generic drugs with complex APIs.

Table 1. *E. coli* proteins and unique peptides identified from FORTEO®

Accession	Description	Unique peptide sequence	PTM	MH+ (Da)	ΔM (ppm)	Rel Ratio* ppm
P60422	50S ribosomal protein L2	SANIALVLYK	N/A	1091.6480	1.86	27
		LEYDPNR	N/A	906.4328	1.31	
		NKDGIPAVVER	N/A	1197.6604	1.46	
P0A7M9	50S ribosomal protein L31	STVGHDLNLDVcSK	C12 (carbamidomethylation)	1544.7428	3.50	8
		YEEITAScScGNVMK	C8 (carbamidomethylation) C10 (carbamidomethylation)	1748.7253	-2.00	

*Rel Ratio in ppm was calculated as the ratio between averaged area under curves (AUC) of all detectable HCP peptides doe the target protein and averaged AUCs of teriparatide tryptic peptides

Figure 1.
MS/MS spectrum of SANIALVLYK of 50S ribosomal protein L2.

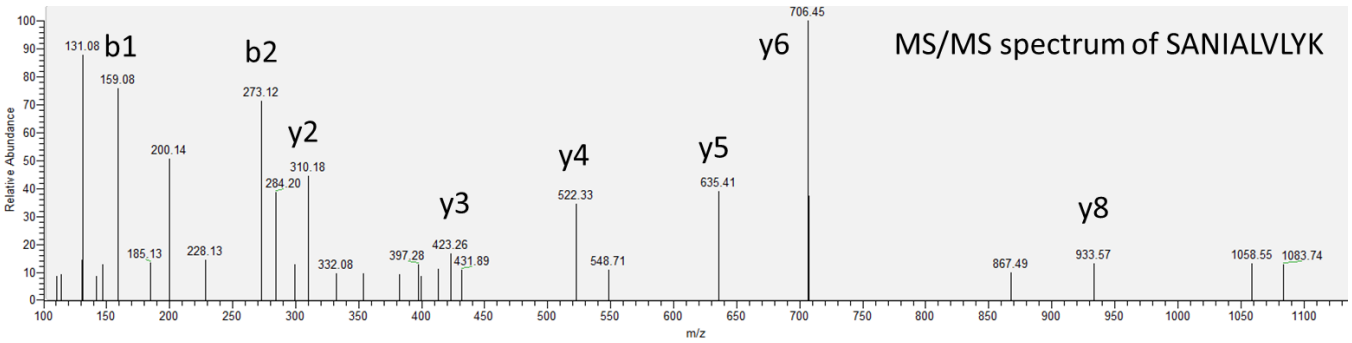
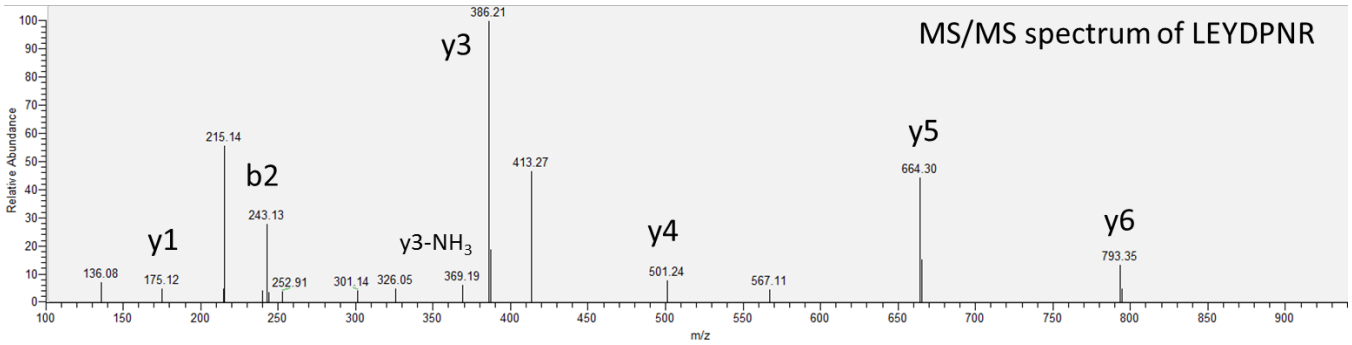


Figure 2. MS/MS spectrum of LEYDPNR of 50S ribosomal protein L2.



Research Projects and Collaborations

New Grants and Contracts

- New Grant (5U01FD004275-07) *Solid State NMR Analysis* with NIPTE
- New Contract (HHSF223201810186C) *In-Silico and in-Vitro Methods for Evaluating Generic Peptide Drug Immunogenicity* with Anne S. De Groot and Cara Depczynski at CUBRC & EpiVax, Inc.

Continuing Grants and Contracts

- Active Contract (HHSF223201610114C) *Mass Spectrometry Profiling of Pentosan Polysulfate in Urine* with John Cort at Battelle Memorial Institute

Active FDA Research

- *Immunogenicity Assays for Peptide Drugs*
- *Solid State Characterization of Polymeric Drugs (Sevelamer)*
- *Evaluation of Immunogenicity Risk from Host Cell Proteins*
- *Impurity Profile Characterization in Synthetic Peptide Drug Products*
- *Characterization of Patiromer Drug Products*

- *Characterization of Conjugated Estrogens*
- *Evaluation of Humanized Mouse Model for Peptide Immunogenicity*
- *Characterization of Synthetic Oligonucleotides and Impurity Profiles to Support Generic Drug Equivalence*

Outcomes

General Guidance

- Draft Guidance on "*ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin*" (October 2017) Link to Posting

Product-Specific Guidances

- *Revised Draft Guidance for Sucralfate Oral Suspension.* FDA Guidance Posting. October 19, 2017. Link to Posting.
- *New Draft Guidance for Soybean Oil Injection Injectable (NDAs 020248, 018449, and 017643)*. FDA Guidance Posting. Feb. 8, 2018. Link to Posting.
- *New Draft Guidance for Soybean Oil Injection Injectable (NDA 019531)*. FDA Guidance Posting. Feb. 8, 2018. Link to Posting.
- *Revised Draft Guidance for Glatiramer Acetate Subcutaneous Injectable*. FDA Guidance Posting. July 20, 2018. Link to Posting.
- *New Draft Guidance for Olive Oil; Soybean Oil Injection Injectable*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.

Publications

- Rathore, D., Faustino, A., Schiel, J., Pang, E., Boyne, M., and Rogstad, S. *The Role of Mass Spectrometry in the Characterization of Biologic Protein Products.* Expert Rev Proteomics. (2018) **15**(5) 431-449. DOI: 10.1080/14789450.2018.1469982. PMID: 29694790.

Presentations

- Jiang, J. *Introduction to Complex Products and FDA Considerations*. Presentation at Public Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. White Oak, MD, Oct. 6, 2017.
- Sasisekharan, R. *Comparative Characterization of Highly Heterogeneous Drugs*. Presentation at Public Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. White Oak, MD, Oct. 6, 2017.
- Verthelyi, D. *Scientific Considerations for the Assessment Immunogenicity Risk of Generic Synthetic Peptide Products*. Presentation at Public Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. White Oak, MD, Oct. 6, 2017.
- Zhang, D. *Demonstrating Complex API Sameness*. Presentation at Public Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. White Oak, MD, Oct. 6, 2017.
- Pang, E. *Scientific and Regulatory Considerations for Synthetic Peptides Referencing Peptide Drug Products of RDNA Origin*. Presentation at 4th USP Workshop on Synthetic Therapeutic Peptides: Regulations, Standards and Quality. Rockville, MD, Nov. 6, 2017.
- Wang, X. *Identification and Quantitation of Host Cell Protein Impurities in Peptide Therapeutics*

Using Liquid Chromatography-Mass Spectrometry. Presentation at 4th USP Workshop on Synthetic Therapeutic Peptides: Regulations, Standards and Quality. Rockville, MD, Nov. 6, 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.
- Jiang, J. *Challenges and Opportunities for Innovation in Complex Generic Drug Product Development*. Presentation at Controlled Release Society (CRS) Annual Meeting. New York, NY, July 22, 2018.
- Jiang, J. *FDA Perspective: FDA Guidance Document and Current Thinking on ANDAs for Certain Highly Purified Synthetic Peptide*. Presentation at Canadian Society for Pharmaceutical Sciences (CSPS) and Health Canada joint Workshop on Complex Formulations. Ottawa, CN, Sept. 10, 2018.
- Zhang, D. *Considerations in Demonstrating Complex API Sameness*. Presentation at Complex Generic Drug Product Development Work- shop. Silver Spring, MD, Sept. 12, 2018.

Posters

- Hu, P., Zhang, D., Kozak, D., and Jiang, X. *Scientific Considerations for Synthetic Peptides Referencing Peptide Drugs of RDNA Origin*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Kedia, K., Bilbao, A., Zhou, M., Payne, S. H., and Cort, J. R. *Universal Open-Source Software for Detecting Metabolites in Complex Mixtures by Scanning Precursors with Predetermined Neutral Lossed from MS/MS*. Poster Presentation at 14th Annual Conference of the Metabolomics Society. Seattle, WA, June 24, 2018.
- Wang, X., Pang, E., Jiang, X., and Rogstad, S. *Identification and Quantitation of Host Cell Protein Impurities in Peptide Biotherapeutics Using Liquid Chromatography-Mass Spectrometry*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.
- Zeng, K., Pang, E., and Keire, D. *Develop and Validate a LC-MS Method to Establish Impurity Profile in the RLD for Teriparatide*. Poster Presentation at FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations. Silver Spring, MD, Oct. 6, 2017.
- Zeng, K., Pang, E., and Keire, D. *Therapeutic Teriparatide Peptides Quality Control by Liquid Chromatography Mass Spectrometry*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 12, 2017.
- Zeng, K., Pang, E., Keire, D., Wang, X., and Rogstad, S. *Therapeutic Teriparatide Peptides Quality Control by Liquid Chromatography Mass Spectrometry*. Poster Presentation at the 66th American Society for Mass Spectrometry (ASMS) Conference. San Diego, CA, June 3, 2018.