Scientific Considerations for Synthetic Peptides Referencing Peptide Drugs of rDNA Origin
P. Hu, D. Zhang, D. Kozak, X. Jiang
U.S. Food and Drug Administration

Purpose
Peptide drugs have become popular candidates for drug development because of their higher affinity, higher specificity and fewer side effects compared to small molecule drugs. Over the years, FDA has approved many peptide drugs in a wide range of therapeutic areas, including diabetes, cancers, osteoporosis and gastrointestinal diseases. In general, these peptide drugs are either made synthetically, through solid phase peptide synthesis (SPPS), or with recombinant DNA technology (rDNA). Recently, with advances in SPPS and analytical technologies, there has been an increased interest from the generic drug industry to manufacture rDNA peptides through SPPS. In order to respond to the demand, we evaluated the scientific bases for the proposed manufacturing switch - whether the current scientific methods are sufficient to characterize the sameness of active ingredients and the equivalence of drug products produced by rDNA technology and SPPS.

Methods
To reference a drug product of rDNA origin with a synthetic peptide using the 505(j) pathway under FD&C Act, the applicant must demonstrate, among other things, that the synthetic peptide has the same active ingredient and is pharmaceutically equivalent and bioequivalent to the reference listed drug (RLD) of rDNA origin. We limited our analysis to five such peptide products (Teriparatide, Glucagon, Liraglutide, Nesiritide and Teduglutide). Since they are all parenteral solutions, and therefore are eligible for a waiver of bioequivalence testing, the main focus will be demonstrating the active ingredient sameness and thus pharmaceutical equivalence between the synthetic peptide drugs and the peptides of rDNA origin in the RLDs. Peptides can be characterized by their primary sequences including amino acid compositions, optical purities and physicochemical properties, as well as their secondary structures, oligomers and aggregation states. Their activity can be evaluated by biological assays. However, peptides are also known to be immunogenic. Due to manufacturing differences, a proposed synthetic peptide may have different impurity profiles, especially peptide-related impurities when compared to the RLD product. Thus, it is crucial to have sensitive methods for peptide impurity analysis. We performed in-depth research using publically available information and results generated by FDA laboratories to evaluate whether currently available methods are sufficient to address the aforementioned issues.

Results
Our analysis found that the amino acid sequences and chemical structures of the five RLD peptide products were clearly defined in their corresponding drug labels without any heterogeneity introduced by post translational modifications (e.g., glycosylation). Thus, current analytical characterizations, including but not limited to peptide mapping, amino acid analysis, mass spectrometry, NMR and HPLC, are sufficient to establish the active ingredient sameness. Unlike peptides of rDNA origin, synthetic peptides do not contain impurities from host-cell proteins that pose immunogenicity concerns, but currently cannot be fully characterized by analytical methods. Thus, the major potential difference in impurity profiles concerns peptide-related impurities. Based on our internal laboratory studies, such differences can be fully characterized.

Conclusion
Active ingredient sameness of peptide drug products with different manufacturing processes can be established using currently available characterization methods. Peptide drugs produced with rDNA technology may have different impurity profiles compared to peptides by chemical synthesis. With the development of highly efficient purification processes, highly sensitive analytical methods, and non-clinical immunogenicity assays, the impurities in the synthetic peptide drugs can be analyzed and controlled to a level at which the immunogenicity risk is comparable to that of RLD products.