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Scientific Considerations for Synthetic Peptides Referencing Peptide Drugs of rDNA Origin

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2017 AAPS ANNUAL MEETING & EXPOSITION

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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

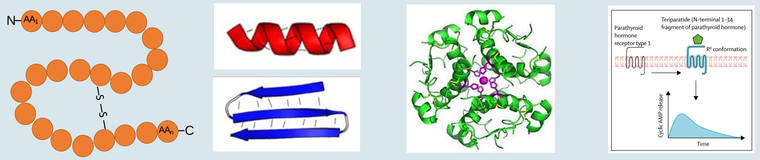
To reference a drug product of rDNA origin with a synthetic peptide using the 505(j) pathway under FD&C Act, the applicant must demonstrate, among other things, that the synthetic peptide has the same active ingredient and is pharmaceutically equivalent and bioequivalent to the reference listed drug (RLD) of rDNA origin. We limited our analysis to five such peptide products (Glucagon, Liraglutide, Nesiritide, Teduglutide and Teriparatide). 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.

Summary of the Five NDA Peptide Drugs of rDNA Origins

Drug Name	Brand Name	NDA #	NDA Holder	Approval Date	Size (amino acid)	Pharmacologic Group
Glucagon	GLUCAGEN	020918	Novo Nordisk	06/22/1998	29	Antihypoglycemic agent and gastrointestinal motility inhibitor
Liraglutide	VICTOZA	022341	Novo Nordisk	01/25/2010	31	Glucagon-like peptide-1 receptor agonist
Nesiritide	NATRECOR	020920	Scios	08/10/2001	32	Natriuretic peptide
Teduglutide	GATTEX	203441	NPS	12/21/2012	33	Glucagon-like peptide-2 analog
Teriparatide	FORTEO	021318	Lilly	06/25/2008	34	Human parathyroid hormone analog

Evaluations of Active Ingredient Sameness in Peptide Drug Products

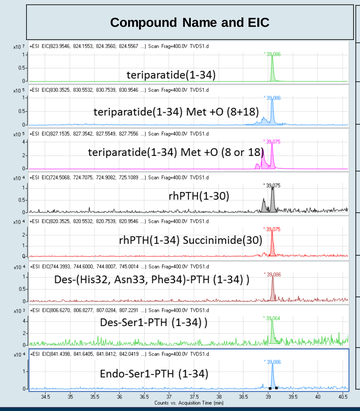
The sameness of active ingredient in a proposed peptide drug can be established through physicochemical characterizations and biological evaluations via orthogonal analytical methods for the following properties:



Primary Sequence and Physiochemical Properties	Secondary Structure	Oligomer/Aggregate States	Biological Activities
↓	↓	↓	↓
LC-MS/MS, Peptide Mapping, Amino Acid Analysis, Optical Purity, etc.	Circular Dichroism, 2D-NMR, etc.	Size Exclusion Chromatography, Analytical Ultracentrifugation, Mass Spectrometry, etc.	Binding and Functional Assays, etc.

Characterization of Peptide-related Impurities in Peptide Drug Products

Peptide-related Impurities includes amino acid sequences related to, but different from, that of the active ingredient, as a result of insertion, deletion, or other modifications (such as oxidation or glycosylation) to the amino acid sequence, and residues of the peptide. Below is an example of a LC-HRMS analysis of FORTEO (teriparatide) showing the characterizations of the active ingredient and the peptide-related impurities (unpublished data from internal research).



Compound Name and EIC	Compound Type	Monoisotope MW	$[M+5H]^{5+}$
teriparatide(1-34)	Active ingredient	4115.131	824.033
teriparatide(1-34) Met +O (8+18)	Modification: Oxidation	4147.120	830.431
teriparatide(1-34) Met +O (8 or 18)	Modification: Oxidation	4131.125	827.232
rhPTH(1-30)	Truncation	3617.892	724.586
rhPTH(1-34) Succinimide(30)	Modification: Succinimidation	4097.120	820.431
Des-(His32, Asn33, Phe34)-PTH (1-34))	Deletion	3716.960	744.399
Des-Ser1-PTH (1-34))	Deletion	4028.099	806.627
Endo-Ser1-PTH (1-34)	Insertion	4202.163	841.439

Available Non-clinical Assessments for Immunogenicity Risks Associated with Peptide-related Impurities

Methods	Features
In Silico Prediction	• Different *in silico* tools that predict binding to major histocompatibility complex (MHC) • High-throughput screening of partial and complete sequences of peptides • Identify potentially immunogenic regions • Map individual amino acid that may contribute to the immunogenic potential of the cluster • Evaluate the immunogenic potential of T-cell epitope clusters for i) individuals of different MHC ii) potential cross-reactivity with non-redundant peptides
In Vitro/Ex Vivo Assay	• Mimic *in vivo* immune process (e.g., binding and functional assays) • Can be used alone or as validation for *in silico* prediction • Innate Immune response modulating impurities (IIRMI) can be assessed by peripheral blood mononuclear cell (PBMC) or cell lines • Cell-lined based methods may be useful in detecting a broad spectrum of IIRMI with careful method validation
Animal Model	• Recent developed humanized mouse models may be applied, but more research and development is required i) Transgenic mice expressing human HLA II, APCs that can respond to "human" epitopes ii) Mice engrafted with human tissues express a repertoire of human immune cells

Recommendations for Synthetic Peptide ANDAs Referencing the Peptides of rDNA Origin[1]

ANDA Submission of Highly Purified Synthetic Peptide Drug Products Referencing Peptide Drugs of rDNA Origin

Pharmaceutical Equivalence

API Sameness

- Primary sequence and physiochemical properties
- Secondary structure
- Oligomer/Aggregation states
- Biological activities (by *in vitro* or animal studies)

Impurities not affecting safety and effectiveness

- Identify each peptide-related impurity that is ***0.10%*** of the drug substance or higher
- Ensure each peptide-related impurity that is found in both generic and RLD, the level in generic peptide is ***not more than*** that in the RLD
- New specified peptide-related impurity is ***not more than 0.5%*** of the drug substance with justifications
- FDA may recommend additional studies

Bioequivalence

Eligible for Biowaiver if the formulation is Q1/Q2 the same as the RLD

REFERENCE

[1] FDA Draft Guidance for Industry: *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin;* October 2017

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.

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