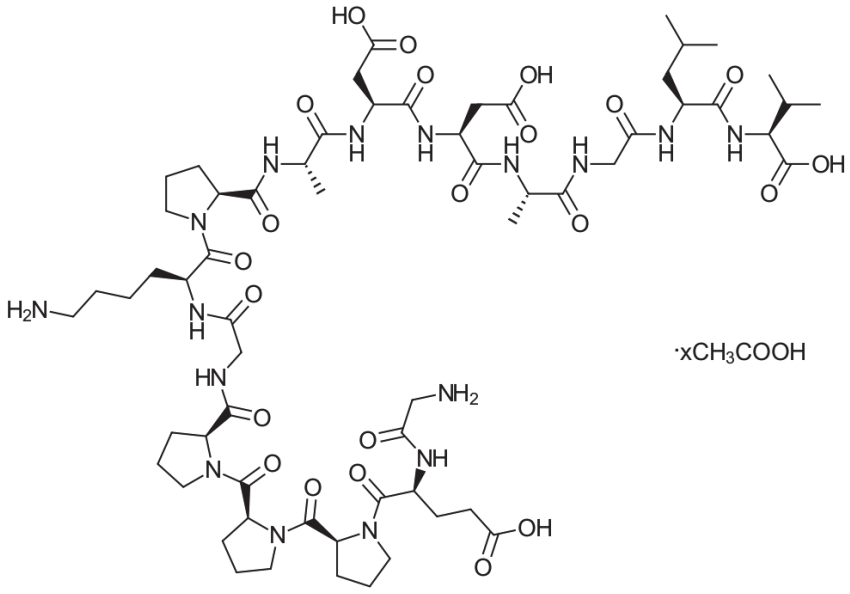
Appendix B: Peptide Identities and Justifications for Placement of Peptide Bulk Drug Substances Under the Enforcement Discretion Policy Regarding 503A Compounding Using Certain Peptide Bulk Drug Substances

---

BPC-157 Identity

BPC-157 Acetate has a molecular formula (MF) of $C_{62}H_{98}N_{16}O_{22}{\cdot}xCH_3COOH$ and a molecular weight (MW) of 1419.54 + x(60.05) g/mol. Its amino acid (AA) sequence is H-Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val-OH·xCH_3COOH and its chemical structure is shown below:

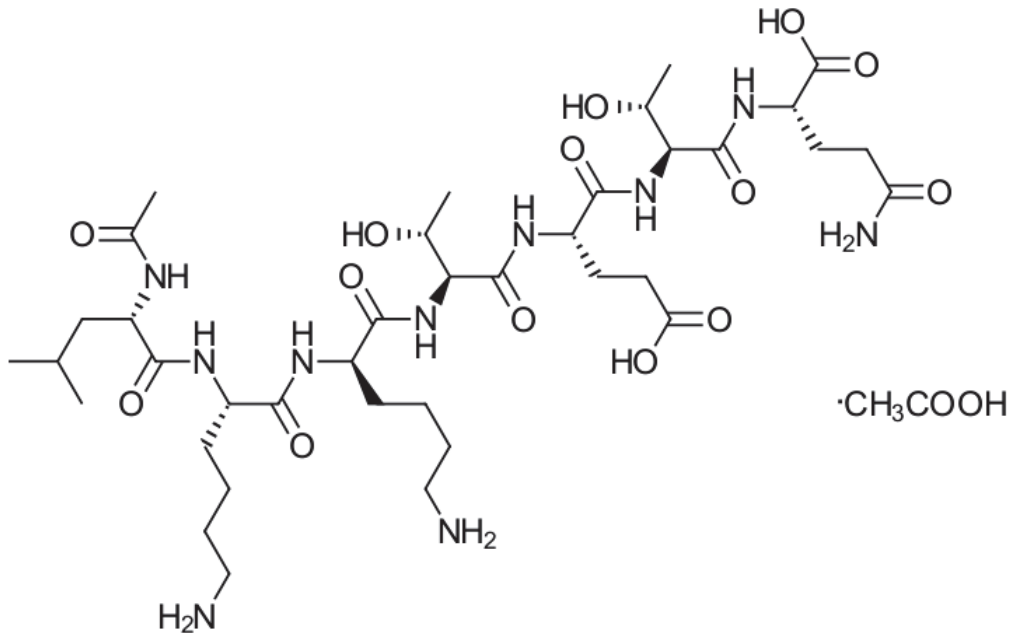


BPC-157 (free base) and BPC-157 acetate were in Category 2 from September 2023 until April 22, 2026, and neither the placement nor the removal changed their status under section 503A; Center for Drug Evaluation and Research (CDER) recommended against listing either form, and the Pharmacy Compounding Advisory Committee (PCAC) voted in favor of inclusion. HHS's justification for including BPC-157 on the interim policy is threefold. First, historical use is now documented and quantified showing its use as well as multiple human studies. Second, the characterization record now includes evidence that was not before CDER, namely a lot-specific certificate from an FDA-registered facility

reporting the identity, impurity, endotoxin, microbial, and residual solvent results CDER found lacking. Third, the conditions of this policy address the risks through lot-level testing, single-active pharmaceutical ingredient (API) products, and MedWatch reporting. Based on the identified updated information, enforcement discretion for BPC-157 acetate is appropriate for subcutaneous, intramuscular, oral, and topical dosage forms that are compounded from API accompanied by a certificate of analysis (CoA) meeting the conditions of this policy.

TB-500 Identity

TB-500 Acetate has a MF of $C_{38}H_{68}N_{10}O_{14}\cdot CH_3COOH$ and has a MW of 949.1 g/mol. Its AA Sequence is Ac-Leu-Lys-Lys-Thr-Glu-Thr-Gln-OH·CH_3COOH and its chemical structure is shown below:

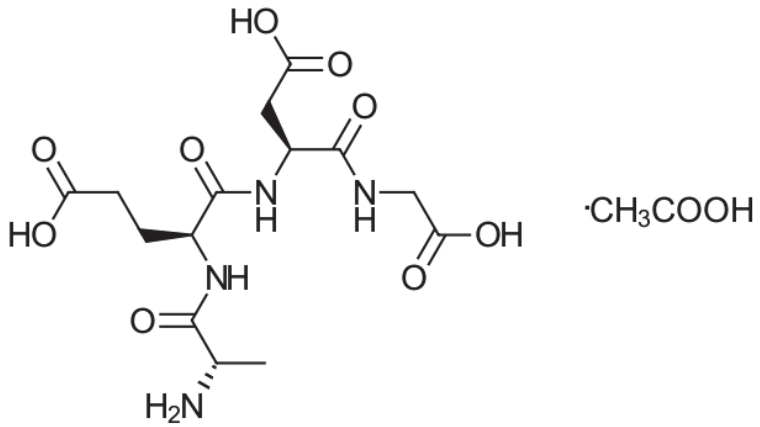


TB-500 was in Category 2 from September 29, 2023, until April 22, 2026, and neither the placement nor the removal changed its status under section 503A; CDER recommended against listing either form, and the PCAC voted in favor of both forms. HHS's justification for including TB-500 on the interim policy is threefold. First, the characterization record has materially changed since the memorandum, as lot-specific certificates from FDA-registered manufacturers supply the identification, assay, impurity, endotoxin, microbial, and residual solvent results CDER found missing. Second, historical use is now

documented and quantified, where CDER could not identify any pharmacy compounding TB-500. Third, the safety concerns CDER identified are inferential rather than observed, the parent protein has a controlled human safety record across several routes, and the fragment is rapidly truncated in human serum. Based on the identified updated information, enforcement discretion for TB-500 acetate appropriate for subcutaneous or intramuscular injectable dosage forms that are compounded from API accompanied by a CoA meeting the conditions of this policy.

Epitalon Identity

Epitalon Acetate has MF of $C_{14}H_{22}N_4O_9 \cdot CH_3COOH$ and has a MW of 450.40 g/mol. Its AA Sequence is H-Ala-Glu-Asp-Gly-OH·CH_3COOH and its chemical structure is shown below:

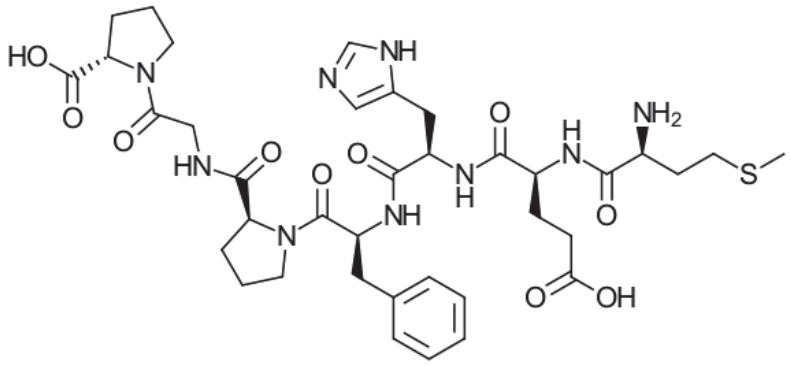


Epitalon was in Category 2 from September 29, 2023, until April 22, 2026, and neither the placement nor the removal changed its status under section 503A; CDER recommended against listing either form, and the PCAC voted in favor of inclusion. HHS's justification for including epitalon on the interim policy is threefold. First, the characterization record has materially changed since the memorandum, as lots from FDA-registered facilities report the endotoxin, microbial, and residual solvent results CDER found missing, and a second lot adds solubility and elemental impurity results that answer CDER's remaining concerns. Second, historical use is now documented and quantified, where CDER had found compounding but could not characterize its extent. Third, CDER's safety concerns are mechanistic rather than based on observed harm, the limited controlled human exposure reported no side effects, and the documented regimens are intermittent rather than continuous. Based on the identified updated information, enforcement discretion for epitalon acetate is appropriate subcutaneous or intramuscular injectable dosage forms that are dispensed in intermittent courses that are compounded from API accompanied by

a CoA meeting the conditions of this policy.

Semax Identity

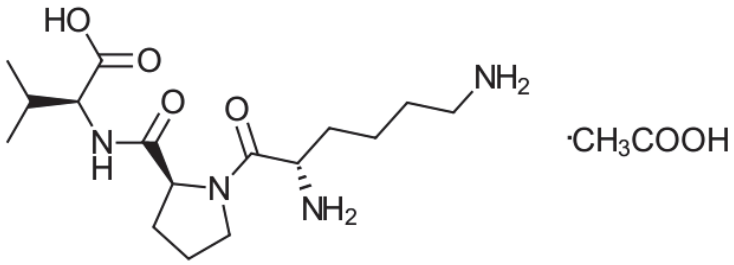
Semax (Free Base) has a MF of $C_{37}H_{51}N_9O_{10}S$ and has a MW of 813.9 g/mol. Its AA sequence is H-Met-Glu-His-Phe-Pro-Gly-Pro-OH and its chemical structure is shown below:



Semax was in Category 2 from September 29, 2023, until April 22, 2026, and neither the placement nor the removal changed its status under section 503A; CDER recommended against listing either form, and the PCAC voted in favor of both forms. HHS's justification for including semax on the interim policy is threefold. First, the characterization record has materially changed since the memorandum, as certificates from FDA-registered sources supply the endotoxin result CDER identified as the principal deficiency for injectable use, together with identity, purity, quantified impurities, residual solvents, and a declared salt form. Second, historical use is now documented and quantified, where CDER had found the extent unclear. Third, the safety concerns CDER identified are mechanistic rather than observed, as the intranasal human record CDER itself compiled covers several hundred subjects with no reported adverse outcome and the bleeding and abuse-potential signals have no clinical counterpart in that record. Based on the identified updated information, enforcement discretion for semax free base is appropriate for intranasal use that is compounded from API accompanied by a CoA meeting the conditions of this policy.

KPV Identity

KPV Acetate has a MF of $C_{16}H_{30}N_4O_4 \cdot CH_3COOH$ has a MW of 402.5 g/mol. Its AA sequence is H- Lys-Pro-Val-OH $\cdot CH_3COOH$ and its chemical structure is shown below:

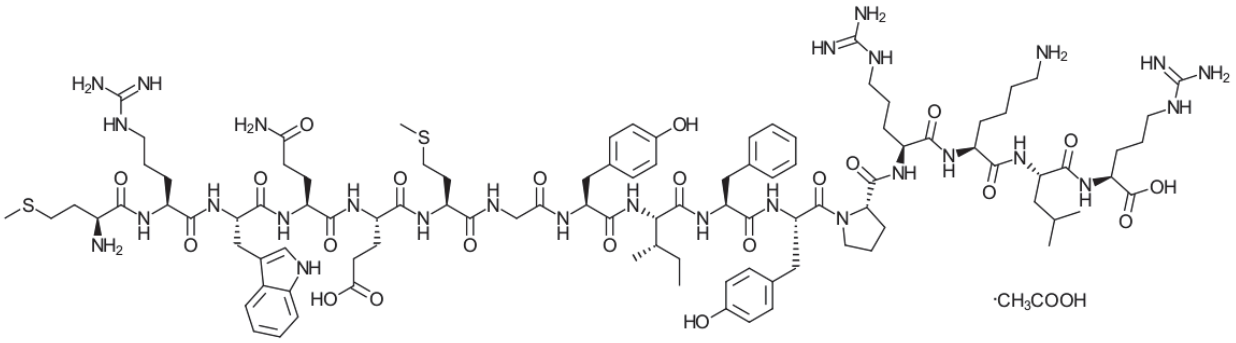


KPV (free base) and KPV acetate were in Category 2 from September 2023 until April 22, 2026, and neither the placement nor the removal changed their status under section 503A; CDER recommended against listing either form, and the PCAC voted in favor of inclusion. HHS's justification for including KPV on the interim policy is threefold. First, historical use is now documented and quantified, including substantial single-ingredient use of the kind this policy covers, where CDER had found the extent of use unknown. Second, the characterization record has materially changed for the acetate, as lots supplied to 503A pharmacies confirm the active moiety by mass spectrometry, report the endotoxin and microbial results CDER found missing, and are consistent with the form for which CDER identified no solubility obstacle. Third, CDER's safety conclusion reflects an absence of information rather than an observed signal, and the conditions of this policy address it through single-API products, lot-level testing, and MedWatch reporting. Based on the identified updated information, enforcement discretion for KPV acetate is appropriate for topical and oral dosage forms that are compounded from API accompanied by a CoA meeting the conditions of this policy.

MOTS-c Identity

MOTS-c Acetate has a MF of $C_{101}H_{152}N_{28}O_{22}S_2 \cdot CH_3COOH$ and a MW of 2234.64 g/mol. Its AA sequence is H-Met-Arg-Trp-Gln-Glu-Met-Gly-Tyr-Ile-Phe-Tyr-Pro-Arg-Lys-Leu-Arg-OH $\cdot CH_3COOH$ and its chemical structure is shown below:

$\cdot CH_3COOH$



MOTS-c was in Category 2 from September 29, 2023, until April 22, 2026, and neither the placement nor the removal changed its status under section 503A; CDER recommended against listing either form, and the PCAC voted in favor of both forms. HHS's justification for including MOTS-c on the interim policy is threefold. First, the characterization record has materially changed since the memorandum, as lot-specific certificates from FDA-registered manufacturers report the impurity, residual solvent, endotoxin, and microbial results CDER found missing and declare the acetate salt form. Second, historical use is now documented and quantified, with the great majority of documented use being single-ingredient products. Third, the available safety evidence points in one direction, as a randomized placebo-controlled trial of a MOTS-c analogue reported no serious adverse events at an exposure well above the compounded regimen and the rodent studies reported metabolic benefit without systemic toxicity. Based on the identified updated information, enforcement discretion for MOTS-c acetate is appropriate subcutaneous or intramuscular injectable dosage forms that are compounded from API accompanied by a CoA meeting the conditions of this policy.

Testing Standard for Peptides Used in Compounding

API and Manufacturer(s) Information[1]

Property/ Quality Attribute	Analytical Method[2]	Acceptance Criteria/ Limit	Relevant Regulatory References
Physicochemical Properties	Orthogonal[3] analytical methods. Refer to Table 1 for acceptable orthogonal methods.	Comply	ICH Q6A

Identification/ Primary sequence	Orthogonal analytical methods. Refer to Table 1 for acceptable orthogonal methods.	Comply with ICH Q6A for identification; verified to be the BDS listed in this guidance	USP <1503>
Higher Order Structure (for complex peptides 8 amino acids or larger)	Orthogonal analytical methods. Refer to Table 1 for acceptable orthogonal methods.	Comply	USP <1503>
Aggregates (for complex peptides 8 amino acids or larger)	Orthogonal analytical methods. Refer to Table 1 for acceptable orthogonal methods.	Comply	USP <1503>
Assay (Drug Substance)	High-Performance Liquid Chromatography (HPLC) / Reversed-Phase High-Performance Liquid Chromatography (RP-HPLC) based on comparison with an established quantitative reference standard	Comply	USP <621>
Biological Activity / Bioassays (for complex peptides 8 amino acids or larger)	Orthogonal analytical methods. Refer to Table 1 for acceptable orthogonal methods.	Comply	USP <1503>
Immunoassay	*In vitro* adaptive and innate immunogenicity assays Enzyme-linked immunosorbent assay (ELISA) Surface Plasmon Resonance (SPR)	Comply	FDA guidance for industry: *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014)
Peptide Content (Net)	Quantitative Amino Acid Analysis (AAA)	Comply	USP <1052>, <507>
	Nitrogen analysis (elemental, Kjeldahl, or HPLC-chemiluminescence nitrogen detector (CLND))	Comply	USP <461>
	UV Spectroscopy	Comply	USP <197>, <857>
	Quantitative Nuclear Magnetic Resonance (qNMR)	Comply	USP <761>, <1761>
Host cell-related impurities (for	Orthogonal analytical methods to characterize the BDS. Refer to Table	Comply	

recombinant product)	1 for acceptable orthogonal methods.		
Peptide-related impurities a) Individual specified impurity b) Any unspecified impurity b) Total impurities	Orthogonal analytical methods to characterize the BDS. Refer to Table 1 for acceptable orthogonal methods.	Comply with ICH Q3A	USP <1503>
Nitrosamine Impurities	Nitrosamine drug substance-related impurities (NDSRI) when applicable (in the presence of secondary, tertiary, or quaternary amines)	Comply with CDER Nitrosamine Impurity Acceptable Intake Limits	FDA guidance for industry: *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)*
	Small molecule Nitrosamines	Comply with CDER Nitrosamine Impurity Acceptable Intake Limits[5]	FDA guidance for industry: *Control of Nitrosamine Impurities in Human Drugs*
Non-peptide-related impurities			
Residual Solvents	Gas chromatography (GC)	Comply with USP <467>, ICH Q3C(R7)	USP <467>, ICH Q3C(R7)
Elemental Impurities	Inductively Coupled Plasma Mass Spectrometry (ICP-MS)	Comply with USP <232>, <233>, ICH Q3D(R1)	USP <232>, <233>, <1065>, ICH Q3D(R1)
Residual TFA	Ion chromatography (IC)	Comply	USP <503.1>, USP <1065>
Residual Fluoride	Ion-selective electrodes	Comply	USP <1065>
Counter-ion Content	Acetate	Comply	USP <503>
	Other anions, cations	Comply	USP <1065>
Water Content	Karl Fischer titration	Comply	USP <921>
Thiol groups (Required only if Cysteine is present)	Ellman's test Liquid chromatography-mass spectrometry (LC-MS)	Comply	USP <736>, Ellman, G. L. (1959). Tissue sulfhydryl groups. *Archives of Biochemistry and*

			Biophysics, 82(1), 70-77.
Bioburden[4]	Microbial enumeration	Comply with <1111>	USP <61>, <1111>
	Specified microorganisms	Comply with <1111>	USP <61>, <62>, <1111>
Bacterial Endotoxins[4]	Bacterial Endotoxins Test (e.g., LAL testing)	Comply with USP <85>	USP <85>, FDA guidance for industry *Pyrogen and Endotoxins Testing: Questions and Answers (Edition 2)* (March 2026)

[1] Required active pharmaceutical ingredients (APIs) and Manufacturer(s) information includes:

- Bulk drug substance (BDS) name (e.g., USAN, INN, IUPAC)
- Chemical structure, amino acid sequence, molecular formula, molecular weight
- Manufacturer's corporate name, its FDA Establishment Identification (FEI) number, address
- Any firm involved in processing (i.e., purification, sterilization, sizing, milling, etc.), FEI number, address
- Repacker or reprocessor, the laboratory that performed the analysis, if applicable
- Batch number
- Date of synthesis
- Date of release
- Expiration date and/or retest date
- Grade: "Intended for human drug compounding"
- Dosage form: a statement of purpose (i.e., intended dosage form, such as injectable, oral, etc.)
- Storage conditions
- Statement of compliance: (e.g., "This product was manufactured and tested in compliance with CGMP.")
- Dated and signed by authorized personnel of the quality unit(s) and identify the original manufacturer

Guidance regarding current good manufacturing practice (CGMP) and the manufacturing of APIs under an appropriate pharmaceutical quality system should be sourced from the ICH guidances for industry *Q7: Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (November 2020) and the *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients: Questions and Answers* (April 2018).

[2] Analytical testing may be conducted utilizing either established compendial procedures or appropriately validated non-compendial (in-house) procedures. Each COA should identify the analytical method used, including the test method name, test method number, and the document number of the approved method validation report (for in-house methods) or approved method verification report (for compendial methods), demonstrating that the method is suitable for its intended purpose. The COA should also include information on any reference standards utilized during testing. The characterization of these reference standards, specifically concerning identity and purity, should be conducted in accordance with ICH Q7.

[3] Orthogonal analytical methods consist of at least two independent analytical procedures relying on distinct physicochemical principles, which should be utilized to provide robust characterization of the BDS.

[4] These criteria are Critical Quality Attributes (CQAs) specific to injectable dosage forms, which should be the standard route of administration (ROA) for peptides due to their low oral bioavailability. If the BDS is intended for incorporation into an alternative dosage form, the appropriate quality tests specific to that dosage form should be conducted and the results reported on the COA.

[5] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits/.

Table 1: Acceptable orthogonal analytical methods to characterize and verify the properties of experimental peptides.

Property/ Quality Attribute	Analytical Method	Relevant References
Physicochemical Properties	Visual inspection for appearance and color	
	Specific optical rotation	USP <781>
	Solubility[1]	
	Isoelectric point (pI) by gel electrophoresis	USP <1053>
	Thermal analysis by differential scanning calorimetry (DSC), differential thermal analysis (DTA), or hot-stage microscopy	USP <891>
	Polymorphic form by Powder X-ray Diffraction (PXRD)	
	Collisional cross section by Ion Mobility Spectrometry (IMS)	
	Particle size distribution	
Identification/ Primary sequence (100% sequence coverage)	HPLC coelution with reference standard	USP <621>
	MS for monoisotopic mass	USP <736>
	Quantitative AAA	USP <1052>, USP <507>
	Tandem MS (MS-MS) sequencing	USP <736>
	NMR Spectroscopy	USP <761>
	Enantiomeric purity	USP <621>, USP <736>
	LC-MS/MS	USP <736>
	N-Terminal sequence analysis / Edman degrada ction	
	Peptide mapping by chemical/enzymatic cleavage	USP <1055>
Higher Order Structure (for complex peptides 8 amino acids or larger)	Circular dichroism (CD)	
	NMR spectroscopy	
	Fourier-transform infrared spectroscopy (FTIR)	
Aggregates (for complex peptides 8 amino acids or larger)	Size-exclusion chromatography (SEC)	
	SEC-multi-angle light scattering (SEC-MALS)	
	Analytical ultracentrifugation (SV-AUC)	
	Dynamic light scattering (DLS)	
	Field-flow fractionation (FFF)	
	IMS	
Biological Activity/ Bioassays (for complex peptides 8 amino acids or larger)	In vitro cell-based assays	ICH Q6B, USP <1032>, <1033>, <1034>
	Ligand- or receptor-binding methods	ICH Q6B, USP <1032>, <1033>, <1034>
	LC-MS, LC-MS/MS	

Peptide-related impurities (including chemical structures)	HPLC/UHPLC spiking with synthesized analogs or isolation/AAA/LC–MS or LC–MS/MS	
	HPLC/UHPLC spiking with synthesized diastereomeric analogs or (sequence specific byproducts and degradation products)	
	Ultra-High Performance Liquid Chromatography-High Resolution Mass Spectrometry (UHPLC-HRMS)	
	Hydrophilic Interaction Liquid Chromatography-Mass Spectrometry (HILIC-MS)	
	Capillary Electrophoresis-Mass Spectrometry (CE-MS)	
Host cell-related impurities (for recombinantly produced peptides)	ELISA	
	LC-MS	

[1] These criteria are Critical Quality Attributes (CQAs) specific to injectable dosage forms, which should be the standard route of administration (ROA) for peptides due to their low oral bioavailability. If the BDS is intended for incorporation into an alternative dosage form, the appropriate quality tests specific to that dosage form should be conducted and the results reported on the COA.