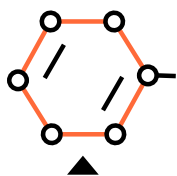




USP Peptide Standards and Materials

Ensuring the identity, quality, purity, and consistency of medication is fundamental to protecting public health. USP’s peptide and excipient monographs, chapters, reference standards and new analytical reference materials give peptide manufacturers confidence when developing and manufacturing these important medicines. USP supports the complete peptide manufacturing workflow with guidance and reference products – from raw materials qualification and testing, through final drug product development, packaging, and distribution.

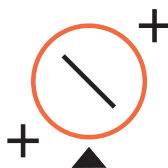
Peptide components



Peptide API



Raw materials



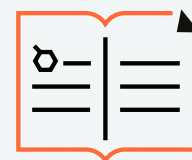
Impurities



Excipients

For general guidance on creating peptide therapies or common methods used to control the quality of peptide products, refer to the following USP general chapters:

- [<1503> Quality Attributes of Synthetic Peptide Drug Substances](#)
- [<1504> Quality Attributes of Starting Materials for the Chemical Synthesis of Therapeutic Peptides](#)
- [<1052> Biotechnology-derived Articles—Amino Acid Analysis](#)
- [<503> Acetic Acids in Peptides](#)
- [<503.1> Trifluoroacetic Acid \(TFA\) in Peptides](#)



USP currently supports the following 19 peptide therapies, with official monographs published in the *USP-NF*. To support the development and manufacturing of these peptide therapies, USP also offers reference standards or analytical reference materials for peptide-specific APIs, process-related or degradant impurities, and excipients present in commercially available formulations.

Bivalirudin	Eptifibatide	Leuprolide	Semaglutide
Calcitonin	Exenatide	Liraglutide	Teriparatide
Corticotropin	Glucagon	Octreotide	Triptorelin
Cosyntropin	Gonadorelin	Oxytocin	Vasopressin
Desmopressin	Goserelin	Protamine	

Additional guidance relevant to peptide therapeutics

1. Bacterial Endotoxins: [<85>](#) (USP Endotoxin Reference Standard)
2. Nitrosamine Impurities: [<1469>](#)
3. Extractables and Leachables: [<665>](#), [<1663>](#), [<1664>](#)
4. Immunogenicity Assay Design/Validation: [<1106>](#) (Anti-Drug Antibodies); [<1106.1>](#) (Anti-Drug Neutralizing Antibodies).

Free educational resources

- Reference Standards to Support Quality of Synthetic Peptide Therapeutics
- Impurity Control Strategies for Therapeutic Peptides
- Peptides Best Practices on Regulatory & Control Strategies, Analytical Methods, and More
- Manufacturing a peptide therapy – quality standards and tools to help expedite development
- Peptide Manufacturing Workflow Infographic

And many more! Please visit us to read our white papers or watch our webinars



USP Education

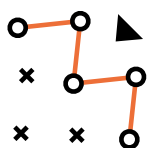
Find trainings

Why do peptide impurities matter?

Controlling peptide-related impurities is essential to meet regulatory requirements and ensure product quality. The presence of impurities in drug substances and finished products can pose significant immunogenicity risks to patients.

Accurate identification and quantification of impurities is required to ensure consistency and reproducibility during manufacturing.

Challenges



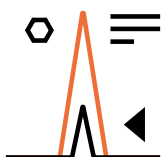
Complex impurity profiles

Peptide synthesis often produces a variety of impurities, including via truncation, deamidation, and isomerization, making detection difficult.



Immune response

Presence of impurities in drug products, if undetected, can trigger immunogenic responses in patients affecting efficacy and safety of the drug



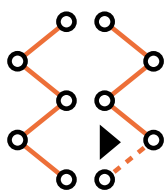
Coelution

Impurities that coelute with either the main peak or other impurities.



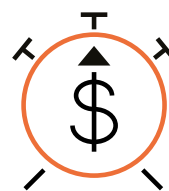
Regulatory compliance

Comprehensive impurity profiling, risk assessments and control strategies are required by regulators.



Separation of closely related or isomeric impurities

Peptide impurities often have similar structures and physicochemical properties, making their detection and quantification challenging and require the advanced and sophisticated methods like LCMS, 2D NMR.



Cost and time

Development of methods for the identification of impurities often requires employing orthogonal analytical tools for accurate and consistent information, impacting the development timelines and cost.



More information: www.usp.org/biologics/peptides

Questions: uspbioinformatics@usp.org

Ordering information: store.usp.org

USP Peptide Impurities Analytical Reference Materials (ARMs)

“ USP ARMs help ensure quality of peptide products ”

USP peptide ARMs can help you overcome analytical challenges

USP ARMs are thoroughly characterized using orthogonal techniques such as LC-MS, NMR, and HPLC, enabling accurate primary structure elucidation and precise detection of impurities to help ensure the quality of peptide drugs.



Complete solution

A comprehensive set of standards for drug substances, drug products monographs, and physical reference materials, including impurities for peptide therapeutics.



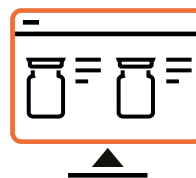
Support for regulatory compliance

Using USP ARMs enables accurate impurity profiling, which can aid in preparing regulatory applications and in demonstrating compliance.



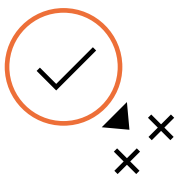
Comprehensive product information sheet

Representative chromatograms and detailed information are provided with ARMs as reference.



Ready availability

ARMs are readily available as catalogued products.



Resolve impurities

Control and monitoring of chemically similar impurities (refers to impurities with similar physicochemical properties to the target peptide. Those are very challenging to quantify and also resolve) is simplified with reference standards, aiding in maintaining high-quality synthetic peptides.



Minimizing risk

Complete impurity profiling using USP standards can help reduce the risk of immune responses to impurities that cannot be detected without the use of standards, thus enhancing the safety profile of peptide therapeutics.

USP-NF Documentary Standards and Proposed Standards	API Reference Standards (USP catalog #)	Impurities (USP catalog #)
<u>Bivalirudin</u> <u>Bivalirudin Injection</u>	Bivalirudin RS (1076013)	Asp9-Bivalirudin RS (1076024) [des-Glu13]-Bivalirudin RS (1076035) [1-11]-Bivalirudin ARM (1800056) [12-20]-Bivalirudin ARM (1800055)
<u>Calcitonin Salmon</u> <u>Calcitonin Salmon Injection</u> <u>Calcitonin Salmon Nasal Solution</u>	Calcitonin Salmon RS (1086200)	Calcitonin Salmon Related Compound A RS (1086210) Calcitonin Salmon Related Compound B RS (1086221) Calcitonin Salmon Trisulfide ARM (1800051) [D-Leu]9-Calcitonin Salmon ARM (1800052) [Des-Tyr]22-Calcitonin Salmon ARM (1800054) [Glu]14-Calcitonin Salmon ARM (1800048) [Glu]20-Calcitonin Salmon ARM (1800047) Parallel Dimer Calcitonin ARM (1800049) [Ser(Ac)]5-Calcitonin ARM (1800050)
<u>Corticotropin Injection</u> <u>Corticotropin for Injection</u> <u>Repository Corticotropin Injection</u>	Corticotropin RS (1149004)	
<u>Cosyntropin</u>	Cosyntropin Acetate RS (1150115)	[Met(O)4]-Cosyntropin ARM (1800057)
<u>Desmopressin Acetate</u> <u>Desmopressin Acetate Injection</u> <u>Desmopressin Nasal Spray Solution</u>	Desmopressin Acetate RS (1173202)	Di-Me-Gly-Desmopressin ARM (1800046)
<u>Eptifibatide*, in PF 50(4)</u>	Eptifibatide RS (1238501)	Eptifibatide dimer RS (1238498) Beta-3-Asp Eptifibatide RS (1238512) D-Har Eptifibatide RS (1238523) 3-D-Asp Eptifibatide RS (1238556) 6-D-Cys Eptifibatide RS (1238578)
<u>Exenatide</u> <u>Exenatide Injection</u>	Exenatide RS (1269105)	[D-His1]-Exenatide RS (1181415) [Glu13]-Exenatide RS (1268998) [Met(O)14]-Exenatide RS (1269009) [N-Acetyl-His1]-Exenatide RS (1269045) C-OH Exenatide ARM (1800035)
<u>Glucagon</u> <u>Glucagon for Injection</u>	Glucagon (HUMAN) RS (1294036)	[Glu]3-Glucagon ARM (1800039) [Glu]24-Glucagon ARM (1800038) [Glu]20-Glucagon ARM (1800040) [Des-Thr]5-Glucagon ARM (1800036) [Met(O)27]-Glucagon ARM (1800037)
<u>Gonadorelin Acetate</u> <u>Gonadorelin Hydrochloride</u> <u>Gonadorelin for Injection</u>	Gonadorelin Acetate RS (1296756) Gonadorelin Hydrochloride RS (1296803)	[D-His2]-Gonadorelin RS (1296701) [D-Tyr5]-Gonadorelin RS (1296712) Gonadorelin Acetate Related Compound A RS (1296767)
<u>Goserelin Acetate</u> <u>Goserelin Implants</u>	Goserelin Acetate RS (1297205)	Goserelin Related Compound A RS (1297216) Goserelin System Suitability Mixture RS (1297250)
<u>Leuprolide Acetate</u>	Leuprolide Acetate RS (1358503)	[Pro(Ac)]1-Leuprolide ARM (1358400) [D-His]-Leuprolide ARM (1358410) [L-Leu]6-Leuprolide ARM (1358430) [D-Ser]-Leuprolide ARM (1358420) [Ser(Ac)]4-Leuprolide ARM (1358440)

USP-NF Documentary Standards and Proposed Standards	API Reference Standards (USP catalog #)	Impurities (USP catalog #)
<u>Liraglutide</u>		[Kyn]31-Liraglutide ARM (1800249) – NEW! Liraglutide Formaldehyde Adduct ARM (1800250) – NEW! [Alpha-Glu(side chain)] Liraglutide ARM (1800251) – NEW! [D-allo-Thr]11-Liraglutide ARM (1800252) – NEW! [D-allo-Thr]13-Liraglutide ARM (1800253) – NEW!
<u>Octreotide Acetate</u>	Octreotide Acetate RS (1477604)	Octreotide Non-Cyclic System Suitability Marker RS (1477615) [Lys(Ac)]5-Octreotide ARM (1477590) Parallel Dimer-Octreotide ARM (1477591) Anti-Parallel Dimer-Octreotide ARM (1477592) [O1(Ac)]8-Octreotide ARM (1009300) [Phe(Ac)]1-Octreotide ARM (1009303) N-Acetyl-Lys-Octreotide Trifluoroacetate ARM (1477690) N-Acetyl-Phe-Octreotide Trifluoroacetate ARM (1477691)
<u>Oxytocin</u> <u>Oxytocin Injection</u>	Oxytocin RS (1491300) Oxytocin Identification RS (1491296)	[Cys(Ac)]1-Oxytocin ARM (1491280) [Asp]5-Oxytocin ARM (1491281) [Glu]4-Oxytocin ARM (1491282) [D-Asp]5-Oxytocin ARM (1491283) Parallel Dimer-Oxytocin ARM (1491284) Anti-parallel Dimer-Oxytocin ARM (1491285)
<u>Protamine Sulfate</u> <u>Protamine Sulfate Injection</u>	Protamine Sulfate RS (1578612)	
<u>Semaglutide</u>		[Beta-Asp]15-Semaglutide ARM (1800243) – NEW! [(Beta-Hydroxybenzyl)-Trp]25-Semaglutide ARM (1800245) – NEW! [Alpha-Glu(side chain)] Semaglutide ARM (1800246) – NEW! [Des-AEEA] Semaglutide ARM (1800254) – NEW!
<u>Teriparatide</u> <u>Teriparatide Injection</u>	Teriparatide RS (1643962)	[MetO8]-Teriparatide ARM (1643970) [MetO18]-Teriparatide ARM (1643971) [Met+O8,18] Teriparatide ARM (1643972)
<u>Triptorelin Pamoate*, in PF 50(3)</u>	Triptorelin Acetate RS (1696131)	Triptorelin Related Compound RSs: A (1696110)/ B (1696128)/ C (1696142)
<u>Vasopressin</u> <u>Vasopressin Injection</u>	Vasopressin RS (1711100) Lypressin RS (1711133)	[Asp]5-Vasopressin ARM (1800045) [Glu]4-Vasopressin ARM (1800041) Parallel Dimer Vasopressin ARM (1800043) Anti-Parallel Dimer Vasopressin ARM (1800044)

* these are not official yet.

Analytical Reference Materials are different from USP Reference Standards and not required for compendial compliance.

Peptide Manufacturing Process

Synthetic peptide drug substances and drug products

