USP Standards to Support Quality of Peptide and Oligonucleotide Therapies

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USP Workshop on Therapeutic Peptides and Oligonucleotides
April 9, 2024

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Agenda

- USP Standard Overview
- USP Peptide Standards
- USP Oligonucleotides Standard Development

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USP Overview

Our enduring mission

To improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.

The USP approach: standard setting

Standard Setting

- **Monographs:** Specifications for pharmaceutical articles in commerce (from release through product shelf life)
- **General Chapters:** General Chapters cover broader topics and more widely applicable methods. These are not linked to individual products unless referenced in a monograph.
- **Physical Reference Standards and Analytical Reference Materials:** Well-characterized materials demonstrated to be suitable for intended use

Collaborating to address shared challenges

Expert volunteers

Provide expertise and enable transparency in the development of quality standards

Regulators

Regulators, including the FDA, depend on a quality-assured scientific basis for decision-making

Industry

Manufacturers depend on validated methods to bring quality pharmaceuticals to market

We recognize and appreciate our volunteers. Public, transparent collaboration through USP

Biologics

- Biologics Monographs 1–Peptides & Oligonucleotides
- Biologics Monographs 2–Proteins
- Biologics Monographs 3–Complex Biologics & Vaccines
- Biologics Monographs 4–Antibiotics
- Biologics Monographs 5–Advanced Therapies

Small Molecules

- Small Molecules 1
- Small Molecules 2
- Small Molecules 3
- Small Molecules 4
- Small Molecules 5
- Over-The-Counter (OTC) Methods & Approaches

Excipients

- Simple Excipients
- Complex Excipients
- Excipients Test Methods

General Chapters

- General Chapters–Dosage Forms
- General Chapters–Chemical Analysis
- General Chapters–Microbiology
- General Chapters–Packaging & Distribution
- General Chapters–Measurement & Data Quality
- General Chapters–Statistics
- General Chapters–Physical Analytics

Healthcare Quality & Safety

- Nomenclature & Labeling
- Healthcare Safety & Quality
- Compounding
- Healthcare Information & Technology

Dietary Supplements & Herbal Medicines, Food Ingredients

- Botanical Dietary Supplements & Herbal Medicines
- Non-Botanical Dietary Supplements
- Dietary Supplements Admission, Evaluation, & Labeling
- Food Ingredients

USP Standards to Therapeutic Support Peptide

USP General Chapters Supporting Peptides

Informational General Chapters	
<1052> *Biotechnology-derived Articles -- Amino Acid Analysis*	<1503> *Quality Attributes Of Synthetic Peptide Drug Substances*

Published in PF 48 (1)
<1504> *Quality Attributes of Starting Materials for the Chemical Synthesis of Therapeutic Peptides*

Procedural General Chapters		
<123> *Glucagon Bioidentity Tests*	<503> *Acetic Acid In Peptides*	<503.1> *Trifluoroacetic Acid (TFA) In Peptides*

USP Peptides Monographs

Drug Substance	Drug Product
Calcitonin Salmon	*Calcitonin Salmon Injection* *Calcitonin Salmon Nasal Solution*
	Repository Corticotropin Injection
Cosyntropin	
Desmopressin Acetate	*Desmopressin Acetate Injection* *Desmopressin Nasal Spray Solution*
Exenatide	*Exenatide Injection*
Glucagon	*Glucagon For Injection*
Gonadorelin Acetate *Gonadorelin Hydrochloride*	*Gonadorelin for Injection*
Goserelin Acetate	*Goserelin Implants*
Leuprolide Acetate	
Octreotide Acetate	
Oxytocin	*Oxytocin Injection*
Teriparatide	*Teriparatide Injection*
Vasopressin	*Vasopressin Injection*

New
Bivalirudin
Bivalirudin for Injection
Eptifibatide
Triptorelin Pamoate

Revision
Glucagon
Gonadorelin Acetate
Teriparatide
Teriparatide Injection

Reporting Threshold in Peptide Monographs

Monograph	Reporting Threshold
Bivalirudin	Procedure 1: s/n >10 Procedure 2: 0.10%
Bivalirudin for Injection	s/n >10
Calcitonin Salmon	Test 1: **0.1%** Test 2: no RT
Eptifibatide future PF	**0.025%**
Exenatide	Procedure 1: 0.05% Procedure 2: 0.05%
Exenatide Injection	0.10%
Glucagon	0.05%
Gonadorelin Acetate	0.05%
Octreotide Acetate	**0.1%**
Triptorelin Pamoate PF	**0.1%**

No Reporting Threshold	No Impurity Test
Cosyntropin	Calcitonin Salmon Injection
Desmopressin Acetate	Calcitonin Salmon Nasal Solution
Glucagon for Injection	Repository Corticotropin Injection
Gonadorelin Hydrochloride	Desmopressin Acetate Injection
Goserelin Acetate	Desmopressin Nasal Spray Solution
Goserelin Implant	Gonadorelin for Injection
Leuprolide Acetate	Oxytocin Injection
Oxytocin	Vasopressin Injection
Teriparatide	
Teriparatide Injection	
Vasopressin	

Guidance on Impurities for Peptides

- ICH Q3A/B Guidance exclude Peptides
- FDA Guidance: ANDAs for Certain Highly Purified Synthetic Drug Products That Refer to Listed Drugs of rDNA Origin (May 2021)
  - Peptide-Related Impurities:
    - Common impurities (including degradants) ≤ RLD
    - New impurities ≤0.5%
    - New impurities 0.10%-0.5% must be identified and justified on the basis of lack of impact on physicochemical properties, biological activity or immunogenicity risk
- EP Substances For Pharmaceutical Use, for Synthetic Peptides, Table 2034

Reporting Threshold	Identification threshold	Qualification threshold
>0.1%	>0.5%	>1.0%

Reporting Threshold Approach for Chemical Derived Drug Substances and Products

- General Chapter revisions related to reporting threshold
  - Revised <1086> Impurities in Drug Substances and Drug Products, PF 45(1), official on May 1, 2021. Exclude peptides.
  - New GC <476> Control of Organic Impurities in Drug Substances and Drug Products, PF 45(1), official on May 1, 2021. Exclude peptides.
  - New General Chapter <477> User-Determined Reporting Thresholds, PF 48(5), to be official on May 1, 2024. Exclude peptides.
- Monograph Approach Example for Chemical Derived Drug Substances and Products
  - Use an appropriate reporting threshold. (See User-Determined Reporting Thresholds ⟨477⟩.) [Note—A reporting threshold of 0.05% may be suitable when the maximum daily dose is ≤2 g.]

Reporting Threshold Feedback

- USP BIO 1 Expert Committee is seeking Feedback on the inclusion of Reporting Thresholds in Monographs
  - Continue providing Reporting Thresholds per current practice
  - Align with approach for Chemical Derived Drug Substances and Products
- Contact Julie Zhang to provide feedback
  - Julie.Zhang@usp.org

USP Reference Standards and Materials

- **Compendial Reference Standards**
  - Specifically linked to methods in the USP-NF
  - Tested in multi-lab studies
  - Approved by the appropriate expert committee
    - Monograph RS, e.g., Insulin Aspart
    - Chapter RS, e.g., mAb IgG System Suitabiliy <129>

- **Non-compendial Reference Standards**
  - Same process as above, but not currently referred to in the USP-NF
  - Details on testing/application included in USP certificate
  - Assay control, control material for method development, standardization testing across laboratories, method transfer
    - USP mAb 001, 002, & 003 Monoclonal IgG1s

- **Analytical Reference Materials (ARMs)**
  - Fit-for-purpose assessment
  - Details on testing/application on Product Information Sheet
    - CHO PLBL2 Host Cell Protein
    - Many more in development-ATCC Partnership

Analytical Reference Materials to Support Peptides Impurities

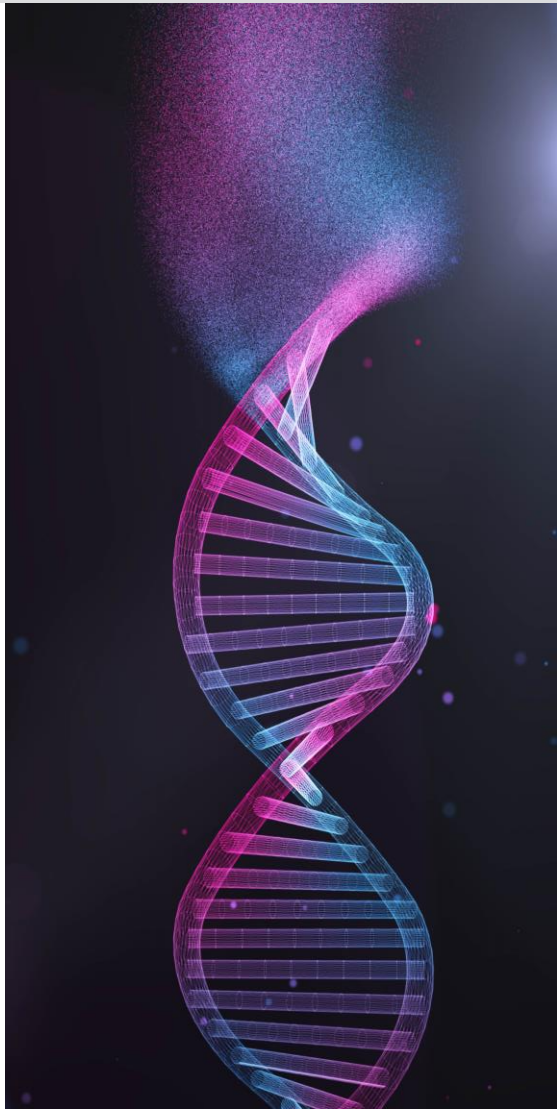
- Materials focused on Process related and Degradation Impurities
- Characterized for Identity and Purity
- Tested by USP compendial Purity method
- Leuprolide, Octreotide, Oxytocin Impurities first released

Test	Results
Appearance	Fine white powder
Identification by IR	Conforms to the Structure
Identification by Mass Spectrometry	Conforms to the Structure
Identification by ^{1}H NMR	Conforms to the Structure
Identification by ^{13}C NMR	Conforms to the Structure
Purity by HPLC	97.5%
Peptide Content by Elemental Analysis (N Determination)	78.89%
TFA Content by HPLC	13.52%
Loss on Drying by TGA	4.06%
Assigned Value *	80.4%

3 USP Standards to Support Therapeutic Oligonucleotides

Oligonucleotide Therapeutics

- Growing Therapeutic Modality
- Includes modified RNA and RNA/DNA hybrids
- Sub-classes include antisense, small interfering RNAs (siRNA) and aptamers
- Mechanisms of action can include splice modulation, RNA interference, RNAse H-mediated cleavage
- Most produced by solid phase synthesis
- 13 products approved by the US FDA between 1998 and 2021



Phosphoramidites - SM for Oligonucleotide Synthesis

- Quality of phosphoramidites or other starting materials (SMs) are vital aspects of the overall oligonucleotide control strategy.
- Deoxyamidites and RNA amidites have been accepted as appropriate SMs for oligonucleotides
- USP has Identified the most common DNA amidites to develop into RS
- Impurities in an amidite have been classified as critical and noncritical. It is crucial that the presence of critical impurities in an amidite be tightly controlled and monitored by appropriate analytical tools

DNA Amidites

dA

dC

dG

dT

5-Me dC

RNA Amidites

rA

rG

rC

rU

USP DNA Amidites RS

- Publicly available DNA amidites produced by industry standard production processes
- Characterized for multiple CQAs
  - They can greatly facilitate development of oligonucleotides
  - Raw materials control

RS Name	Item Number	Lot number	Molecular Formula
iBu dG Beta-Cyanoethyl Phosphoramidite (dG)	1152030	F18040	$C_{44}H_{54}N_7O_8P$
T Beta-Cyanoethyl Phosphoramidite (T)	1152031	F18050	$C_{40}H_{49}N_4O_8P$
Bz dA Beta-Cyanoethyl Phosphoramidite (dA)	1152032	F18060	$C_{47}H_{52}N_7O_7P$
5-Me Bz dC Beta-Cyanoethyl Phosphoramidite (5-Me dC)	1152033	F18070	$C_{47}H_{54}N_5O_8P$
Bz dC Beta-Cyanoethyl Phosphoramidite (dC)	1152034	F191A0	$C_{46}H_{52}N_5O_8P$

Extensively Characterized for Physicochemical Attributes

- Rigorously tested and evaluated in inter-laboratory studies
- Reviewed and approved by Expert Committee

Attributes	Methods
Appearance	Visual
Identification	^{1}H NMR
	LC-MS
Purity/Impurity	HPLC
	^{31}P NMR
Residual Solvent	*USP <467> GC*
Water	*USP <921> Karl Fischer*
Hygroscopicity	*Vapor Sorption*

More Phosphoramidites Standards to Come

Other Standards under Development

- RNA Phosphoramidites Standards
- MOE Phosphoramidites Standards
- Documentary Standards
  - Validated Identification and Purity methods

Expert Volunteers help power USP's impact on global public health

Serving on Expert Committees, Panels and Sub-Committees, they collaborate to develop quality standards and other solutions that help build a more resilient supply of quality medicines.

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