FDA Briefing Document

Pharmacy Compounding Advisory Committee (PCAC) Meeting

July 23 -24, 2026

The attached package contains background information prepared by the Food and Drug Administration (FDA or Agency) for the panel members of the Pharmacy Compounding Advisory Committee (advisory committee). We are bringing certain compounding issues to this advisory committee to obtain the advisory committee's advice. The background package may not include all issues relevant to the final committee recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

MOTS-c-Related Bulk Drug Substances (MOTS-c (free base) and MOTS-c acetate)

Table of Contents

FDA Evaluation of MOTS-c – Related Bulk Drug Substances (MOTS-c (free base) and MOTS-c acetate)

DATE: 5/11/2026

FROM: Jing Li, Ph.D.
Chemistry reviewer, Office of Product Quality Assessment II (OPQAII), Office of Pharmaceutical Quality (OPQ)

Nga-Lai Poon, Pharm.D.
Regulatory Specialist, Office of Compounding Quality and Compliance (OCQC), CDER, Office of Compliance (OC)

Kemi Asante, Pharm.D., M.P.H., RAC
Lead Consumer Safety Officer, OCQC, OC

Edna Albuquerque, Ph.D.
Senior Pharmacology/Toxicology Reviewer, Division of Pharmacology/Toxicology for Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine (DPT-RPURM/SM), Office of New Drugs (OND)

Andrea Benedict, Ph.D.
Nonclinical Team Leader, DPT-RPURM/SM, OND

Marianne San Antonio, D.O.
Physician, PCRT, OSM, OND

Suhail Kasim, M.D., MPH
Lead Physician, PCRT, OSM, OND

THROUGH: Russell Wesdyk, M.S., M.B.A.
Associate Director Regulatory Affairs, OPQA2, OPQ

Alex Gorovets, M.D.
Deputy Director, OSM, OND

Matt Lash, J.D.
Acting Director, OCQC, OC
Deputy Director, OC

TO: Pharmacy Compounding Advisory Committee

SUBJECT : Evaluation of MOTS-c-related Bulk Drug Substances (MOTS-c (free base) and MOTS-c acetate) for Inclusion on the 503A Bulk Drug Substances List

List of Abbreviations

Abbreviation	Term
AMPK	adenosine monophosphate-activated protein kinase
API	active pharmaceutical ingredient
AT1R	angiotensin II type 1 receptor
BDS	bulk drug substance
BET	bacterial endotoxins test
BMM	bone marrow macrophage
CoA	Certificate of Analysis
ETβR	endothelin β receptor
FAERS	FDA Adverse Event Reporting System
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
Global DRO	Global Drug Reference Online
INN	International Non-proprietary Name
IP	intraperitoneal
IUPAC	International Union of Pure and Applied Chemistry
IV	intravenous
MOTS-c	Mitochondrial Open Reading Frame of the 12S rRNA-c
NF	National Formulary
OF	outsourcing facility
OVX	ovariectomy
ROA	route of administration
SC	subcutaneous
UHMWPE	ultra-high molecular weight polyethylene
USAN	United States Adopted Name
USP	United States Pharmacopeia

I. INTRODUCTION

The Food and Drug Administration (FDA, the Agency, or we) received a nomination for Mitochondrial Open Reading Frame of the 12S rRNA-c (MOTS-c)-related bulk drug substances (BDSs) for inclusion on the list of BDSs that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[1] The nominator of MOTS-c-related BDSs provided inconsistent information in the nomination package regarding the specific BDS proposed. Specifically, it is unclear in the nomination package whether the nomination was for MOTS-c (free base) or MOTS-c acetate. MOTS-c (free base) and MOTS-c acetate are different pharmaceutical ingredients and hence are considered different BDSs. Please see additional information in Section II.A. The nomination was withdrawn[2], and FDA is evaluating the substances at its discretion.

MOTS-c is reported to be a peptide consisting of 16 amino acids. Although it is unclear whether the nominator intended to nominate MOTS-c (free base) or MOTS-c acetate, FDA has decided to evaluate both on its own initiative.

MOTS-c-related BDSs were nominated for the following uses: insulin resistance, obesity, osteoporosis, vascular calcification, muscle/fat metabolism, longevity.[3,4] The MOTS-c-related drug products proposed in the nomination are 5 mg and 10 mg for subcutaneous (SC) injection.

There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for MOTS-c (free base) or its acetate form, and neither is a component of an FDA-approved drug.

We have evaluated publicly available data on the physicochemical characteristics, historical use, safety, and effectiveness in compounding of these substances. For the reasons discussed below, we believe the evaluation criteria ***weigh against*** placing MOTS-c (free base) or MOTS-c acetate

---

[1] The nomination of "Mitochondrial Open Reading Frame of the 12S rRNA-c (MOTS-c)" was submitted by Wells Pharmacy Network (Wells) (Document ID: FDA-2015-N-3534-0293) and can be accessed at: https://www.regulations.gov/document/FDA-2015-N-3534-0293. The nomination was withdrawn, but because FDA is evaluating MOTS-c (free base) and MOTS-c acetate on its own initiative, FDA considered information submitted in this nomination as part of this evaluation.

[2] Document ID: FDA-2015-N-3534-0484.

[3] We have explained that it is necessary to evaluate a nominated bulk drug substance in the context of the uses proposed for compounded drug products that include the substance, though we acknowledge that inclusion of a substance on the 503A Bulks List may not be limited to a specific use. See 84 FR 4696, 4701.

[4] FDA did not evaluate the proposed uses: insulin resistance, obesity, osteoporosis, vascular calcification, muscle/fat metabolism, longevity because the nomination did not include sufficient information for the Agency to evaluate whether the substance is appropriate for these uses in compounded drug products. In addition, FDA did not identify clinical studies evaluating these uses of MOTS-c. See 80 FR 65765 for the information necessary to fully evaluate a substance for inclusion on the 503A Bulks List.

on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act (503A Bulks List).

II. EVALUATION CRITERIA

A. Is the Substance Well-Characterized, Physically and Chemically?[5]

MOTS-c is a common name and not a United States Adopted Name (USAN).[6] FDA has encountered multiple salts, and derivatives, including different active moieties, sold commercially under the same common name for similarly situated products. Inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., INN[7], IUPAC[8], USAN) represent a safety risk for patients as they may be dosed with a different BDS than the physician ordered. From a chemical analysis standpoint, inconsistent naming conventions for MOTS-c related BDSs also introduce risks because of the inability to determine which BDS a particular reference standard is referencing.

A BDS or active pharmaceutical ingredient (API)[9] used in a drug product may be a free base (i.e., the native molecule) or a salt or an ester of the free base, all of which share the same active

---

[5] Among the conditions that must be met for a drug compounded using bulk drug substances to be eligible for the exemptions in section 503A of the FD&C Act is that the bulk drug substances are manufactured by an establishment that is registered under section 510 of the FD&C Act and that each bulk drug substance is accompanied by a valid certificate of analysis. Sections 503A(b)(1)(A)(ii) and (iii). A bulk drug substance is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice. Section 501(a)(2)(B).

[6] United States Adopted Name (USAN) is a unique, nonproprietary name for a drug sold in the United States. The USAN Council, which is sponsored by several organizations, assigns USANs. This program and naming convention are intended to help physicians, pharmaceutical manufacturers of active ingredients and finished dosage forms, and pharmacists ensure that the patient is provided with the drug the physician intended.

[7] International Nonproprietary Names (INN) facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic name.

[8] The International Union of Pure and Applied Chemistry (IUPAC) is an international federation of National Adhering Organizations working for the advancement of the chemical sciences, especially by developing nomenclature and terminology.

[9] The terms BDS and active pharmaceutical ingredient (API) are used interchangeably in the compounding context. See 21 CFR 207.3 ("*Bulk drug substance*, as referenced in sections 503A(b)(1)(A) and 503B(a)(2) of the Federal Food, Drug, and Cosmetic Act, previously defined in § 207.3(a)(4), means the same as "active pharmaceutical ingredient" as defined in § 207.1."). An API is defined in FDA regulations at 21 CFR 207.1, which states "*Active pharmaceutical ingredient* means any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. Active pharmaceutical ingredient does not include intermediates used in the synthesis of the substance."

moiety.[10] Different active moieties are not interchangeable because they can have different safety and efficacy profiles. Similarly, a free base or the various salts or ester of an active moiety are distinct chemical entities, each with a different chemical structure and unique physical/chemical, or pharmacokinetic/pharmacodynamic characteristics. As a result, each may offer distinct properties (e.g., different solubilities, permeability, melting points, stability, or flow characteristics) and may also have different safety and/or efficacy profiles. All distinct active moieties, as well as free bases, salts, or esters of any given active moiety, are distinct BDSs for these reasons.

MOTS-c is a 16-amino-acid peptide encoded by a short open reading frame (sORF) within the mitochondrial 12S rRNA (mitochondrial open-reading-frame of the twelve S rRNA type-c) (Zheng et al. 2023). As discussed above, FDA received a nomination for MOTS-c related BDSs that were not clear whether the intended nomination was for MOTS-c (free base) or MOTS-c acetate salt. These substances are distinct BDSs/APIs. Therefore, for the purpose of this assessment, we will consider both MOTS-c (free base) and MOTS-c acetate and will evaluate the physical and chemical characterization of each.

Table 1 below summarizes available identifying information obtained from the public domain for each BDS.

Table 1. Summary of Basic Information on MOTS-c (Free Base) and MOTS-c Acetate.

	MOTS-c (Free Base)	**MOTS-c Acetate**
UNII Code	A5CV6JFB78	Not available
CAS No.*	1627580-64-6	CAS number of the free base is used
MF/MW (g/mol)	$C_{101}H_{152}N_{28}O_{22}S_2$/2174.6	$C_{101}H_{152}N_{28}O_{22}S_2 \cdot xCH_3COOH$/NA
Peptide sequence	H-Met-Arg-Trp-Gln-Glu-Met-Gly-Tyr-Ile-Phe-Tyr-Pro-Arg-Lys-Leu-Arg-OH	H-Met-Arg-Trp-Gln-Glu-Met-Gly-Tyr-Ile-Phe-Tyr-Pro-Arg-Lys-Leu-Arg-OH x·CH_3COOH
Supplier[11]	Yes	Yes
Active moiety	MOTS-c (free base)	MOTS-c (free base)

* CAS is an abbreviation of Chemical Abstracts Service. MF = molecular formula. MW = molecular weight.

One nomination was submitted, which, as discussed above, was later withdrawn. The nominator provided inconsistent information about the different MOTS-c BDSs in their nomination package. Due to inconsistencies in the nomination, it is unclear which MOTS-c-related BDS the

[10] "*Active moiety* is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance."21 CFR 314.3.

[11] The existence of a supplier of BDS may be relevant to FDA's characterization analysis because it indicates that consistent production of the BDS according to a standard may be possible. BDSs with suppliers are also frequently accompanied by COAs associated with their production, which can help FDA to identify and characterize BDSs.

nominator intended to nominate. For example, the Certificate of Analysis (CoA) submitted with the nomination package refers to one BDS by name in the title and a different BDS by the CAS number. All chemistry related information about the BDSs provided by nominator is summarized in Table 2.

Table 2. Summary of Information Submitted in the Withdrawn Nomination.

Nominator	1
Nominated BDS	MOTS-c
BDS per UNII code	A5CV6JFB78 *(matches MOTS-c free base)*
CoA	CoA provided for MOTS-c Acetate
CAS No.	1627580-64-6 *(matches MOTS-c free base)*
MF	$C_{101}H_{152}N_{28}O_{22}S_2$ *(provided in the nomination package that matches MOTS-c free base)*
MW (g/mol)	Not provided
Chemical name	(4*S*)-4-[[(2*S*)-5-amino-2-[[(2*S*)-2-[[(2*S*)-2-[[(2*S*)-2-amino-4-methylsulfanylbutanoyl]amino]-5-carbamimidamidopentanoyl]amino]-3-(1*H*-indol-3-yl)propanoyl]amino]-5-oxopentanoyl]amino]-5-[[(2*S*)-1-[[2-[[(2*S*)-1-[[(2*S*,3*S*)-1-[[(2*S*)-1-[[(2*S*)-1-[(2*S*)-2-[[(2*S*)-1-[[(2*S*)-6-amino-1-[[(2*S*)-1-[[(1*S*)-4-carbamimidamido-1-carboxybutyl]amino]-4-methyl-1-oxopentan-2-yl]amino]-1-oxohexan-2-yl]amino]-5-carbamimidamido-1-oxopentan-2-yl]carbamoyl]pyrrolidin-1-yl]-3-(4-hydroxyphenyl)-1-oxopropan-2-yl]amino]-1-oxo-3-phenylpropan-2-yl]amino]-3-methyl-1-oxopentan-2-yl]amino]-3-(4-hydroxyphenyl)-1-oxopropan-2-yl]amino]-2-oxoethyl]amino]-4-methylsulfanyl-1-oxobutan-2-yl]amino]-5-oxopentanoic acid *(matches MOTS-c free base)*

Italics in the table above represents the information identified by the FDA.

FDA is choosing to concurrently evaluate both BDSs (MOTS-c free base and MOTS-c acetate) in this section under two different sub-sections (II.A.1 and II.A.2) and will provide a separate conclusion for each of the two BDSs.

The nominator has proposed to compound this BDS into the following dosage form:

- Injection
  - For an injection product, in general, critical quality attributes (CQAs) including sterility, bacterial endotoxins test (BET), and foreign particulates are considered critical safety factors. For this reason, microbial bioburden load (i.e., microbial enumeration test) and BET are critical for the BDSs to be used in compounding injections. Evaluation of the solubility of the BDS is also considered critical to ensure that no BDS precipitates are formed in the compounded drug product.

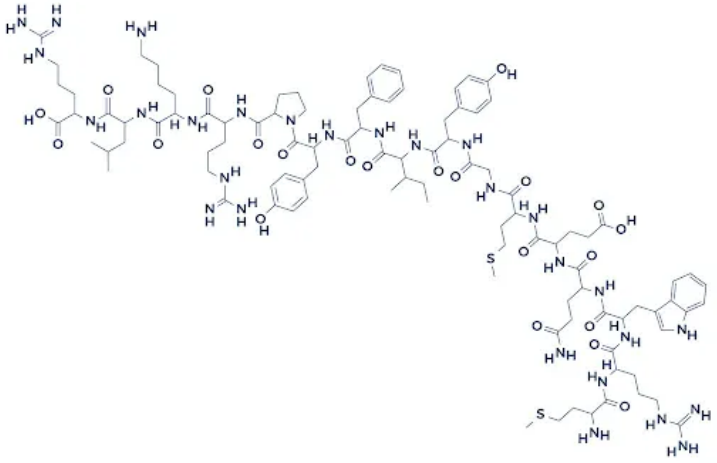
There is no USP drug substance monograph for MOTS-c (free base) or its acetate salt. We reviewed physical and chemical characterization-related information provided by the nominator and performed a literature search for additional information on MOTS-c (free base) and its acetate salt. Databases searched for information on MOTS-c (free base) and its acetate salt in

preparation of this section included SciFinder, Analytical Profiles of Drug Substances, PubMed, the European Pharmacopoeia, and the USP-NF.

1. *MOTS-c (Free Base)*

MOTS-c is reported to be a synthetic version of a mitochondria-derived 16-amino acid peptide encoded by the open reading frame of the 12S rRNA type C (Lee et al. 2016). The molecular formula of MOTS-c (free base) is $C_{101}H_{152}N_{28}O_{22}S_2$ with the molecular weight of 2174.6 g/mol. The chemical structure and peptide sequence of MOTS-c are shown in Figure 1. There is no CoA available for MOTS-c (free base) in the nomination.

Figure 1. The Chemical Structure[12] and Peptide Sequence[13] of MOTS-c (Free Base).
Chemical Structure of MOTS-c:



Sequence:

H-Met-Arg-Trp-Gln-Glu-Met-Gly-Tyr-Ile-Phe-Tyr-Pro-Arg-Lys-Leu-Arg-OH

a. Stability of the Active Pharmaceutical Ingredient and Likely Dosage Forms

It is reported that lyophilized MOTS-c (free base) is stable when stored at -20°C desiccated and protected from light in a tightly closed container.[14] Upon reconstitution, the solution is recommended to keep/store at +4°C between 2-7 days and for future use below -18°C.[15]

FDA notes that peptides can be extremely sensitive to product formulation, process, and environmental conditions (e.g., pH, heat (temperature), concentration, in-process related impurities, excipients etc.), which may lead to the aggregation and degradation of peptides. This could result in loss of their biological activity (Zapadka et al. 2017). Multiple analytical methods

[12] https://www.peptides.org/mots-c/. Accessed March 21, 2025.
[13] https://pubchem.ncbi.nlm.nih.gov/compound/146675088#section=Biologic-Description. Accessed March 21, 2025.
[14] https://www.anaspec.com/assets/b2f60ab5-a1f5-4201-9a1b-435a9bcf7abc/sds-en-as-65587-mots-c.pdf. Accessed March 21, 2025.
[15] https://www.prospecbio.com/mots-c. Accessed March 21, 2025.

may be needed to detect various aggregates, including size exclusion chromatography or field flow fractionation. Hence, peptides may require more and/or specific analytical in-process and finished product testing for impurities than what is required for small molecules. Uncontrolled manufacturing processes as well as impurities may increase the risk of product aggregation, especially for MOTS-c (free base) with 16-amino acids. Significant amounts of aggregates can form in formulated products, especially during storage or when exposed to stress conditions. Therefore, product formulation is critical to the quality and stability of peptide drug products, as it is necessary to maintain the peptide molecules in their native state (in the formulation) to the extent possible.

b. Probable Routes of API Synthesis

MOTS-c (free base) can be synthesized using a standard Fmoc-based solid phase synthesis methodology, as described by Jiang (Jiang et al. 2021). Then, the obtained crude peptide was purified by preparative High-Performance Liquid Chromatography (HPLC). The purity of the peptide was determined by analytical HPLC and Electrospray Ionization Time-of-Flight (ESI-TOF) Mass Spectrometry (ESI-TOF MS). There are other possible synthesis paths as well, which would result in different impurity profiles. It is difficult to know which synthesis pathways are used by chemical suppliers of the nominated MOTS-c (free base).

c. Likely Impurities[16]

Generally speaking, peptide-related impurities and peptide synthesis process-related impurities contribute to and are considered in understanding the impurity profile for all peptides, including MOTS-c (free base). For most synthetic peptides, solid-phase peptide synthesis method has been widely used by industry for peptide synthesis. The solid phase synthesis of peptides may lead to potential peptide-related impurities due to incomplete coupling reactions, truncations, or side reactions. These peptide-related impurities are typically similar in structure to the target peptide and may be difficult to identify and quantify without sophisticated analytical methods. Additional potential common impurities may be derived from impurities in the protected amino acid starting materials (e.g., isomeric impurities and free amino acids) and other species that may carry over into drug substances. In addition, residual solvents, coupling reagents, activators, catalysts, and scavengers may exist as solid phase peptide synthesis process related impurities. Drug substance and its proposed product-related impurities may also include peptide-related aggregates.

There is no CoA for MOTS-c (free base) in the nomination package. We conducted literature searches and found a CoA for MOTS-c (free base) that only contains purity testing result shown

[16] This evaluation contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking into account the amount of the impurity, dose, route of administration, and chronicity of dosing. Available nonclinical toxicity data for likely impurities of concern (e.g., nitrosamines, potential mutagenic substances, and potential teratogenic substances) in the nominated bulk drug substance are discussed in the Nonclinical Assessment at Section C.I. as part of the safety assessment of the substance.

below as an example (Figure 2).[17] However, there is no information on the impurity limits/testing results as attribute control in the CoA to demonstrate quality control of impurity profile of MOTS-c (free base).

Because there is lack of information regarding potential impurities that can be present in MOTS-c (free base) and the lack of information on the potential of peptide aggregation, we cannot rule out the potential for immunogenicity associated with these impurities and peptide-related aggregates.

Figure 2. Example of CoA for MOTS-c (Free Base).

Xi 'an genotide bio-technology Co.,Ltd

Certification of Analysis

Product Name	***MOTs***		
Molecular Formula	C101H152N28O22S2	***Batch No.***	
Molecular Weight	*2174.59*	***Manufacturing Date***	
Sequence	H-Met-Arg-Trp-Gln-Glu-Met-Gly-Tyr-Ile-Phe-Tyr-Pro-Arg-Lys-Leu-Arg-OH		

	TEST	***SPECIFICATION***	***RESULT***
1	***Appearance***	*White or slightly yellowish powder*	*Complies*
2	***Identity***	*Monoisotopic Mass: 2174.59±1.0*	*2174.55*
3	***Peptide Purity*** *(By HPLC)*	≥98.0%	*99.67%*
4	***Water Content***	<8.0%	*Not test*
5	***Peptide Content*** *(By N%)*	≥85.0%	*86.0%*
6	*Conclusion*	*Conforms to standard*	*Complies*

Q.C. Manager:xiqing Inspector: Frank Gao

Date:Oct-26,2022

d. Physicochemical Characteristics Pertinent to Product Performance, Such as Particle Size and Polymorphism

MOTS-c (free base) is white to off-white lyophilized powder. Based on the reports in most publicly available literature MOTS-c (free base) is soluble in water[18,19]and in phosphate-buffered saline (Bhullar et al. 2021).

In the nomination package, under "What strength(s) will be compounded from the nominated substance?", it claims as "5 mg and 10 mg Lyophilized Vial". However, there is no information in the nomination about the volume of water or other solvent used to reconstitute the final

[17] https://www.limitlesslifenootropics.com/product/mots-c-10mg/. Accessed March 21, 2025.
[18] https://lifescienceproduction.co.uk/mots-c/. Accessed March 21, 2025.
[19] https://pharmalabglobal.com/product/mots-c-peptide/. Accessed March 21, 2025.

solution for SC administration. MOTS-c is reported to be soluble in water, however there is no solubility data available from public domain or in the nomination for FDA assessment to ensure that the nominated BDS will be completely soluble in the final solution without precipitates formed in the compounded drug product. Because the nominator did not provide any information on how to compound the proposed injectable product with known concentration, we cannot evaluate how the water solubility of MOTS-c (free base) will impact the performance of the proposed injectable final product.

e. Any Other Information About the Substance That May Be Relevant, Such as Whether the API Is Poorly Characterized or Difficult to Characterize

Because there is lack of CoA for MOTS-c (free base), we do not know if microbial bioburden and/or BETs are in place to control the BDS proposed for compounding injectable dosage form. Endotoxin test is considered a critical quality control attribute for injection product. No such relevant information was identified from public domain either.

Conclusions: MOTS-c (free base) is reported to be a peptide consisting of 16 amino acids. As reported in the literature, lyophilized MOTS-c (free base) is expected to be stable when stored below -20°C desiccated and protected from light in a tightly closed container.

Compounded drugs containing MOTS-c (free base) may pose significant risk for immunogenicity when administered by injection routes due to potential of aggregate formation as well as potential peptide-related impurities. The nominator did not provide information regarding the immunogenicity risk of MOTS-c (free base) and FDA identified only limited information in the literature. Because of the lack of information regarding potential impurities that can be present in MOTS-c (free base) and the lack of information on the potential of peptide aggregation, FDA cannot rule out the potential for immunogenicity associated with these impurities and peptide related impurity aggregates.

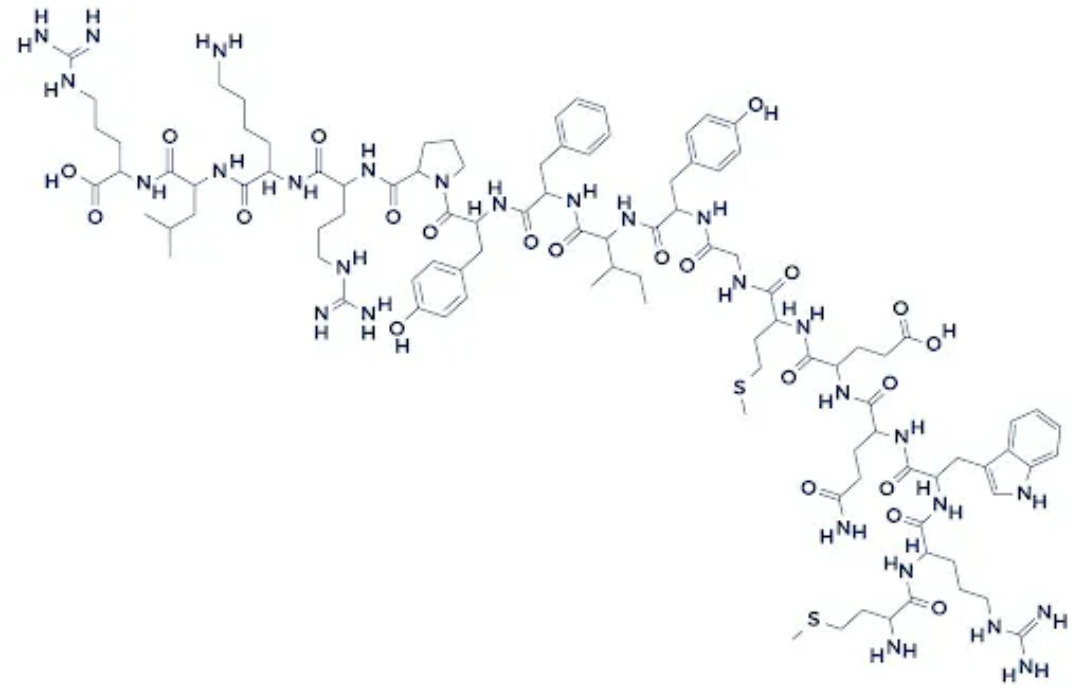
MOTS-c (free base) is considered to be not well-characterized from the physical and chemical characterization perspective because (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., USAN, INN, IUPAC), and (2) BDS specific quality control attributes, including impurities, aggregates, bacterial endotoxins, and microbial bioburden testing, were not found in the publicly available scientific literature and lack of CoA in the nomination package which are offered as evidence to establishing identity, purity, and impurity profiles of the substance. We also note that the stability, pharmacological activity, and immunogenic properties of peptides such as MOTS-c (free base) are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product. In addition, due to lack of information on the water solubility data of MOTS-c (free base) as well as the reconstituted concentration of proposed injectable final product, it is difficult to draw a conclusion if the water solubility of MOTS-c (free base) will be a potential issue to impact product performance for the proposed injectable dosage form.

2. MOTS-c Acetate

The molecular formula of MOTS-c acetate is $C_{101}H_{152}N_{28}O_{22}S_2 \cdot CH_3COOH$ with the molecular weight of 2234.64 g/mol. The chemical structure is shown in Figure 3. The nominator provided CoA for MOTS-c acetate with the quality control attribute testing results, including

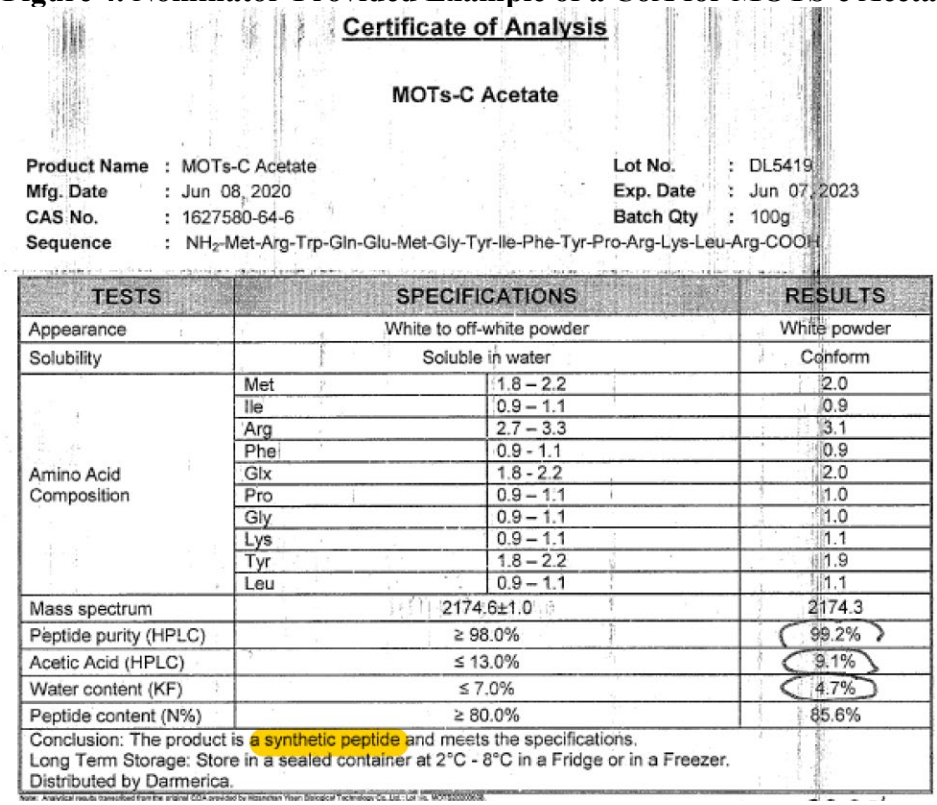
identification, amino acid composition, assay, water content and acetate content (Figure 4). There is no testing result for the quality control attribute on impurities, aggregates, microbial bioburden and/or bacterial endotoxin levels, and residual solvent(s).

Figure 3. The Chemical Structure of MOTS-c Acetate.[20]


·CH_3COOH

[20] https://aapep.bocsci.com/product/mots-c-human-acetate-447759.html. Accessed April 23, 2026.

Figure 4. Nominator-Provided Example of a CoA for MOTS-c Acetate.



Certificate of Analysis

MOTs-C Acetate

Product Name : MOTs-C Acetate
Lot No. : DL5419
Mfg. Date : Jun 08, 2020
Exp. Date : Jun 07, 2023
CAS No. : 1627580-64-6
Batch Qty : 100g
Sequence : NH_2-Met-Arg-Trp-Gln-Glu-Met-Gly-Tyr-Ile-Phe-Tyr-Pro-Arg-Lys-Leu-Arg-COOH

TESTS	SPECIFICATIONS		RESULTS
Appearance	White to off-white powder		White powder
Solubility	Soluble in water		Conform
Amino Acid Composition	Met	1.8 – 2.2	2.0
	Ile	0.9 – 1.1	0.9
	Arg	2.7 – 3.3	3.1
	Phe	0.9 - 1.1	0.9
	Glx	1.8 - 2.2	2.0
	Pro	0.9 – 1.1	1.0
	Gly	0.9 – 1.1	1.0
	Lys	0.9 – 1.1	1.1
	Tyr	1.8 – 2.2	1.9
	Leu	0.9 – 1.1	1.1
Mass spectrum	2174.6±1.0		2174.3
Peptide purity (HPLC)	≥ 98.0%		99.2%
Acetic Acid (HPLC)	≤ 13.0%		9.1%
Water content (KF)	≤ 7.0%		4.7%
Peptide content (N%)	≥ 80.0%		85.6%

Conclusion: The product is a synthetic peptide and meets the specifications.
Long Term Storage: Store in a sealed container at 2°C - 8°C in a Fridge or in a Freezer.
Distributed by Darmerica.

a. Stability of the API and Likely Dosage Forms

Based on the CoA provided by the nominator, long-term storage conditions for MOTS-c acetate are "in a sealed container at 2°C to 8°C". Additionally, MOTS-c acetate is reported to be stable at -80°C for 2 years and at -20°C for 1 year. The aliquot solution of MOTS-c acetate is stable at -80°C for 6 months and at -20°C for 1 month.[21]

FDA notes that peptides can be extremely sensitive to product formulation, process, and environmental conditions (e.g., pH, heat (temperature), concentration, in-process related impurities, excipients etc.), which may lead to the aggregation and degradation of peptides. This could result in loss of their biological activity (Zapadka et al. 2017). Multiple analytical methods may be needed to detect various aggregates, including size exclusion chromatography or field flow fractionation. Hence, peptides may require more and/or specific analytical in-process and finished product testing for impurities than what is required for small molecules. Uncontrolled manufacturing processes as well as impurities may increase the risk of product aggregation. Significant amounts of aggregates can form in formulated products, especially during storage or when exposed to stress conditions. Therefore, product formulation is critical to the quality and stability of peptide drug products, as it is necessary to maintain the peptide molecules in their native state (in the formulation) to the extent possible.

[21] https://www.medchemexpress.com/mots-c-human-acetate.html. Accessed March 21, 2025.

b. Probable Routes of API Synthesis

MOTS-c (free base) can be synthesized using a standard Fmoc-based solid phase synthesis methodology as mentioned in Section A.1.b. Then, the free base can be converted into MOTS-c salt. As mentioned in A1.2, there are other possible synthesis paths as well, which would result in different impurity profiles. It is difficult to know which synthesis pathways are used by chemical suppliers of the nominated MOTS-c acetate.

c. Likely Impurities[22]

Generally speaking, peptide-related impurities and peptide synthesis process-related impurities contribute to and are considered in understanding the impurity profile for all peptides, including MOTS-c acetate. For most synthetic peptides, solid-phase peptide synthesis method has been widely used by industry for peptide synthesis. The solid phase synthesis of peptides may lead to potential peptide-related impurities due to incomplete coupling reactions, truncations, or side reactions. These peptide-related impurities are typically similar in structure to the target peptide and may be difficult to identify and quantify without sophisticated analytical methods. Additional potential common impurities may be derived from impurities in the protected amino acid starting materials (e.g., isomeric impurities and free amino acids) and other species that may carry over into drug substances. In addition, residual solvents, coupling reagents, activators, catalysts, and scavengers may exist as solid phase peptide synthesis process related impurities. Drug substance and its proposed product-related impurities may also include peptide-related aggregates, especially for peptide like MOTS-c acetate with 16-amino acid that may have an inherent tendency to aggregate.

In the CoA the nominator provided there is purity test limit of ≥ 98.0% with the testing result of 99.2% for MOTS-c acetate. However, there is no impurity quality control attribute tests to demonstrate the impurity profiles.

We conducted literature searches and found that most CoA for MOTS-c acetate only contains purity testing result shown below as an example (Figure 5).[23] However, there is no information on the impurity limits/testing results as attribute control in the CoA to demonstrate quality control of impurity profile of MOTS-c acetate.

---

[22] This evaluation contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety and quality issues associated with impurities in a drug product compounded using that bulk drug substance taking into account the amount of the impurity, dose, route of administration, and chronicity of dosing. Available nonclinical toxicity data for likely impurities of concern (e.g., nitrosamines, potential mutagenic substances, and potential teratogenic substances) in the nominated bulk drug substance are discussed in the Nonclinical Assessment at Section C.I. as part of the safety assessment of the substance.

[23] https://file.medchemexpress.com/batch_PDF/HY-P2048A/MOTS-c-human-acetate-COA-66073-MedChemExpress.pdf. Accessed March 21, 2025.

Because there is lack of information regarding potential impurities that can be present in MOTS-c acetate and the lack of information on the potential of peptide aggregation, we cannot rule out the potential for immunogenicity associated with these impurities and peptide related aggregates.

Figure 5. Example of a CoA for MOTS-c Acetate.

MCE MedChemExpress

Certificate of Analysis

MOTS-c(human) (acetate)

Cat. No.:	HY-P2048A
Batch No.:	66073
Chemical Name:	L-Arginine, L-methionyl-L-arginyl-L-tryptophyl-L-glutaminyl-L-α-glutamyl-L-methionylglycyl-L-tyrosyl-L-isoleucyl-L-phenylalanyl-L-tyrosyl-L-prolyl-L-arginyl-L-lysyl-L-leucyl-

PHYSICAL AND CHEMICAL PROPERTIES

Molecular Formula:	$C_{103}H_{156}N_{28}O_{24}S_2$
Molecular Weight:	2234.64
Storage:	Sealed storage, away from moisture Powder -80°C 2 years -20°C 1 year * In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)
Chemical Structure:	

MRWQEMGYIFYPRKLR (acetate salt)

ANALYTICAL DATA

Appearance:	White to off-white (Solid)
LCMS:	Consistent with structure
Purity (LCMS):	98.97%
Conclusion:	The product has been tested and complies with the given specifications.

d. Physicochemical Characteristics Pertinent to Product Performance, Such as Particle Size and Polymorphism

MOTS-c acetate is a white to off-white solid powder. It is reported to dissolve in water at 6.25 mg/mL.[24] Because the nominator did not provide any information on how to compound the proposed injectable product with known concentration, we cannot evaluate how the water solubility of MOTS-c acetate will impact the performance of the proposed injectable final product.

e. Any Other Information About the Substance That May Be Relevant, Such as Whether the API Is Poorly Characterized or Difficult to Characterize

In the CoA the nominator provided, there is no testing result for the quality control attribute on impurities, aggregates, and microbial bioburden and/or bacterial endotoxin levels. Bacterial endotoxin test is considered a critical quality control attribute for injection products. No such relevant information was identified from public domain, either.

[24] https://www.medchemexpress.com/mots-c-human-acetate.html. Accessed March 21, 2025.

Conclusions: MOTS-c acetate is an acetate salt of a peptide consisting of 16 amino acids. As reported in the literature, MOTS-c acetate is expected to be stable under reported storage conditions (below -20°C).

MOTS-c acetate is considered not well-characterized from the physical and chemical characterization perspective because (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., INN, IUPAC, USAN,), and (2) certain critical characterization data specific to MOTS-c acetate (including impurities, aggregates, microbial bioburden and/or bacterial endotoxin) were not found in the publicly available scientific literature, and the provided CoA, which was offered as evidence to establishing identity, purity, and impurity profiles of the substance. The limited information related to critical characterization data is particularly important for immunogenicity. As discussed in Section II.D.2.d., FDA is concerned about the potential for immunogenicity of MOTS-c acetate when formulated in an injectable dosage form for SC administration due to the potential for aggregation as well as potential peptide-related impurities, as discussed in the impurities section. Injectable routes of administration may present a particular risk for immunogenicity. The nomination did not include, and FDA has not identified, information about MOTS-c acetate to suggest that this substance does not present these risks. Therefore, we cannot rule out potential immunogenicity issues associated with peptide and peptide-related impurities aggregates. In addition, we cannot evaluate how the water solubility of MOTS-c acetate will impact the performance of the proposed injectable final product due to lack of information on how to compound the proposed injectable product with known concentration. We also note that the stability, pharmacological activity, and immunogenic properties of peptides such as MOTS-c acetate are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

B. Has the Substance Been Used Historically in Compounding?

MOTS-c related BDSs were nominated for the injectable route of administration and use in insulin resistance, obesity, osteoporosis, vascular calcification, muscle/fat metabolism, longevity; however, FDA searched generally for information on the historical use of MOTS-c (free base) and MOTS-c acetate in compounding. Information about use may not specify specific attributes of the product, such as route of administration. Databases searched for information on both substances for this evaluation included PubMed, EMBASE, Google/Google Scholar, Micromedex, Clinical Pharmacology, NatMedPro Database, USP/NF, European Pharmacopoeia, Japanese Pharmacopoeia, European Medicines Agency, GlobalEdge.com, and the Outsourcing Facility (OF) Product Reporting Database.[25] It is often unclear whether the MOTS-c discussed in information from these sources is the salt form or the free base and whether it was compounded or not. Therefore, FDA will consider the information discussed in this section in its evaluation for both the free base and salt form as appropriate.

1. Length of Time the Substance Has Been Used in Compounding

The nominator did not provide historical use data.

[25] Available at https://dps.fda.gov/outsourcingfacility.

MOTS-c, a peptide containing 16 amino acids encoded by the genic region 12S rRNA mitochondrial or MT-RNR1, was first discovered by Lee et al. in 2015 (Monterio et al. 2019).

The earliest and extent of MOTS-c (free base) or MOTS-c acetate use in compounding is unknown. No published studies were found in which non-compounded or compounded drug products containing MOTS-c (free base) or MOTS-c acetate were used in humans. According to outsourcing facility (OF) reports submitted to FDA, OFs have not reported preparing single or multiple-API compounded drug products containing MOTS-c (free base) or MOTS-c acetate from January 2017 to December 2025.[26]

2. The Medical Condition(s) It Has Been Used to Treat

Results from a Google search indicate that MOTS-c is marketed on websites alone and in combination with other substances.

Several websites assert that MOTS-c is used to regulate mitochondrial energy; promote the metabolism of fatty acid in the liver; promote metabolic homeostasis; improve glucose regulation; aid in the resistance of metabolic stress; protect against insulin resistance; promote weight loss; improve physical performance (Appendix 1); promote muscle health; support DNA repair and autophagy; and slow cellular aging.[27] It is unclear whether compounded products are being used in all of these instances.

3. How Widespread Its Use Has Been

An internet search for compounded drug products containing MOTS-c revealed that a holistic clinic states that they work with compounding pharmacies to obtain compounded peptide drug products containing MOTS-c.[28] A wellness clinic promotes a "Cocktail IV Therapy" that contains MOTS-c but does not provide additional drug product details of the other substances in the compounded drug product (Appendix 2).

MOTS-c appears as a prohibited substance in the Global Drug Reference Online (Global DRO) Database, which obtains information from the 2024 WADA (World-Anti-Doping Agency) Prohibited List of Hormone and Metabolic Modulators.[29]

---

[26] The Drug Quality and Security Act, signed into law on November 27, 2013, created a new section 503B in the Federal Food, Drug, and Cosmetic Act. Under section 503B, a compounder can become an outsourcing facility. Outsourcing facilities are required to provide FDA with a list of drugs they compounded during the previous six- month period upon initial registration and in June and December each year. This retrospective information does not identify drugs that outsourcing facilities intend to produce in the future. https://dps.fda.gov/outsourcingfacility

[27] Renew Youth – MOTS-c: A potential anti-aging peptide. Available at https://www.renewyouth.com/mots-c-a-potential-anti-aging-peptide/. Accessed 3/20/24.

[28] What are Peptides? Available at https://www.hawaiiwholepersonhealing.com/peptides/. Accessed 3/20/24.

[29] Global Drug Reference Online (Global DRO). Available at https://globaldro.com/Home. Accessed 3/20/24.

4. Recognition of the Substance in Other Countries or Foreign Pharmacopeias

A search of the European Pharmacopoeia (11.5 edition, 2024), and the Japanese Pharmacopoeia (18th Edition) did not show any monograph listings for MOTS-c (free base) or MOTS-c acetate. The European Medicines Agency did not list any products containing MOTS-c or MOTS-c acetate that are authorized for use.

Conclusions: It is often unclear whether the MOTS-c discussed in the sources considered for this section is the salt formulation or the free base. Available literature indicates that MOTS-c was discovered by researchers in 2015. Published literature did not reveal studies in which compounded drug products containing MOTS-c or MOTS-c acetate were used in humans. OFs did not report compounding drug products containing MOTS-c or MOTS-c acetate. Based on internet searches, it appears that compounded MOTS-c is marketed alone and in combination with other substances as injectable formulations. MOTS-c is marketed for numerous uses, including regulating mitochondrial energy, promoting the metabolism of fatty acid in the liver; promoting metabolic homeostasis; improving glucose regulation; aiding in the resistance of metabolic stress; protecting against insulin resistance; promoting weight loss, and improving physical performance. In addition, MOTS-c is a prohibited substance on the Global DRO database.

C. Are There Concerns About the Safety of the Substance for Use in Compounding?

1. Nonclinical Assessment

The nominator submitted nonclinical information. Specifically, they submitted 10 articles describing pharmacological studies of MOTS-c (Fuku et al. 2015; Hu and Chen 2018; Kim et al. 2019; Lee et al. 2016; Lee et al. 2015; Lu et al. 2019a; Monteiro et al. 2019; Reynolds et al. 2021; Wei et al. 2020; Yang et al. 2019).

The following databases were consulted in preparation of this section: Drugs@FDA, Embase, European Chemicals Agency, FDA's Generally Recognized as Safe Notice Inventory, Google, Google Scholar, National Institutes of Health's dietary supplement label database, National Toxicology Program website, Pharmapendium, PubMed, Society of Toxicology, USP, and Web of Science.

The studies discussed in this section do not clearly identify the specific form of MOTS-c (free base or salt) used in the different experiments. Therefore, throughout this section, we refer to MOTS-c as it is referred to in the articles.

a. General Pharmacology of the Drug Substance

As described in section II.A, MOTS-c is a naturally occurring mitochondrial hexadecapeptide encoded by a transcript consisting of a 51-base pair short open reading frame within the mitochondrial 12S ribosomal RNA type-c. According to Lee and collaborators, who first sequenced MOTS-c, this mitochondrial peptide appears to be highly conserved across species and is expressed in different tissues, including skeletal muscle, heart, and brain. In addition, MOTS-c is present in the systemic circulation in humans and rodents (Lee et al. 2015). Figure 6 illustrates the sequence of MOTS-c, which is the active moiety of MOTS-c (free base) and MOTS-c acetate.

Figure 6. Amino Acid Sequence of MOTS-c (Excerpted From Knoop et al. 2019).

Left to right: Amino acid sequence from the N- to the C-terminal domain. Arg: arginine; Gln: glutamine; Glu: glutamic acid; Gly: glycine; Ile: isoleucine; Leu: leucine; Lys: lysine; Met: methionine; Phe: phenylalanine; Pro: proline; Trp: tryptophan; Tyr: tyrosine.

Nonclinical pharmacological studies have reported that MOTS-c affects glucose and lipid metabolism, bone remodeling, and the cardiovascular system in in-vivo and in-vitro models. Specifically, as discussed below, synthetic MOTS-c can according to the authors: (i) suppress diet-induced obesity and diet- and age-dependent insulin resistance in mice (Kim et al. 2019; Lee et al. 2015; Lee et al. 2016), (ii) promote osteogenesis in rat bone mesenchymal stem cells (BMSCs) in vitro (Hu and Chen 2018), (iii) inhibit osteolysis in vivo and in vitro (Yan et al. 2019), and (iv) reduce vascular calcification and associated myocardial remodeling in a rat model of vascular calcification (Wei et al. 2020).

MOTS-c on Glucose and Lipid Metabolism

Lee and collaborators reported that adult male CD-1 mice fed a high-fat diet (60% by calories) and treated with intraperitoneal (IP) injections of MOTS-c (0.5 mg/kg/day) for 8 weeks gained significantly less body weight than untreated male mice fed the same diet. At the end of the 8-week treatment, MOTS-c-treated mice weighed ~20% less than vehicle-treated mice. The reduced body weight gain of MOTS-c-treated mice was accompanied by increased energy expenditure and reduced fat accumulation in the liver. In addition, treatment with MOTS-c suppressed the hyperinsulinemia induced by high-fat diet in mice (Lee et al. 2015).

Evidence that MOTS-c can improve insulin sensitivity was obtained from two additional experiments in the study by Lee and collaborators. In one experiment, adult male CD1 mice treated with MOTS-c (5 mg/kg/day, IP) required ~30% higher glucose infusion rate than vehicle-treated mice to maintain euglycemia during insulin stimulation. In addition, the MOTS-c treatment increased insulin-stimulated glucose disposal rate without affecting hepatic glucose production (Lee et al. 2015). In the other experiment, soleus muscles from older (12 months old) male C57/BL6 mice were shown to be more insulin resistant than soleus mice from younger (3 months old) mice, and MOTS-c treatment (5 mg/kg/day, IP) of the older mice restored the insulin sensitivity of their soleus muscles to levels comparable to those of the younger mice. Specifically, ex vivo, insulin (60 μU/ml)-induced 2-deoxyglucose uptake into soleus muscles of 12-month-old mice treated with MOTS-c (5 mg/kg/day; IP) for 7 days was significantly higher than that in soleus muscle from age-matched mice treated with saline and was comparable to that in soleus muscle from 3-month-old mice treated with saline (Lee et al. 2015).

A separate study from the same research group reported that, in 17-week-old male C57/BL6J mice made obese by a high-fat diet, MOTS-c treatment (2.5 mg/kg, IP, twice a day, 3 days) compared to vehicle treatment (water, IP, twice a day, 3 days) significantly reduced (by ~50%) blood glucose levels (Kim et al. 2019). Treatment with MOTS-c also reduced plasma levels of oxidized glutathione in obese mice, a finding suggestive of reduced cellular oxidative stress. In addition, treatment with MOTS-c decreased levels of plasma metabolites associated with three lipid metabolism pathways: sphingolipid metabolism, monoacylglycerol metabolism, and fatty acid dicarboxylate metabolism (Kim et al. 2019).

MOTS-c was shown to prevent obesity and insulin resistance induced by ovariectomy (OVX) in female mice (Lu et al. 2019b). Specifically, ovariectomized mice treated with MOTS-c (5 mg/kg/day, IP) for 12 weeks gained significantly less body weight than saline-treated, ovariectomized mice. In addition, compared to the vehicle treatment, the MOTS-c treatment: (i) increased glucose tolerance in ovariectomized mice, (ii) reduced OVX-induced fat accumulation, (iii) increased brown fat activation in ovariectomized mice, (iv) decreased OVX-induced upregulation of inflammatory cytokines (e.g., interleukin 1β and interleukin 6), and (v) suppressed OVX-induced increase in levels of lipid oxidation markers in white adipose tissue (Lu et al. 2019b).

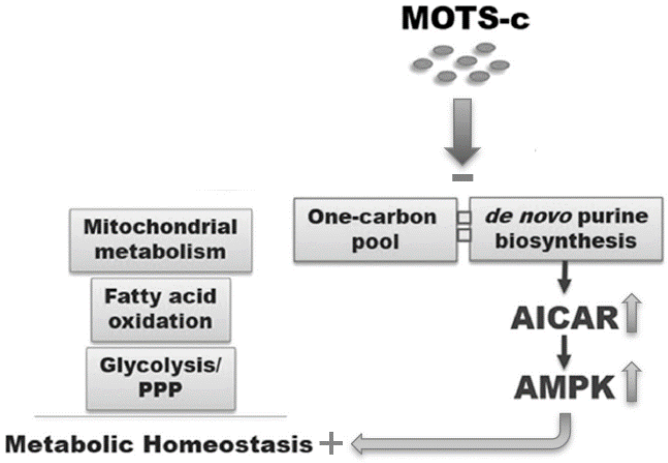
Consistent with the findings that MOTS-c can improve metabolic homeostasis, acute treatment of young (2 months old), middle-age (12 months old), and old (22 months old) CD-1 mice with MOTS-c (5 mg/kg, IP) significantly enhanced their performance in a treadmill (Reynolds et al. 2021). Evidence was also provided that a 2-week treatment of treadmill-exercised old mice with MOTS-c (15 mg/kg/day) compared to an equivalent vehicle treatment increased glucose metabolism and upregulated expression of metabolism-associated genes in the mouse skeletal muscles (Reynolds et al. 2021).

Intermittent treatment with MOTS-c (15 mg/kg; 3x/week) initiated late in the life of male C57BL/6N mice (when the animals were 23.5 months old) increased not only their physical capacity but also their lifespan (Reynolds et al. 2021). The median and maximal lifespans were 912 and 1047 days, respectively, for vehicle-treated mice and 970 and 1120 days, respectively, for MOTS-c-treated mice.

The initial work by Lee and collaborators reported that the effects of MOTS-c on fatty acid oxidation, glycolysis, and insulin resistance in mice fed with high-fat diet could not observed if the animals were also treated with compound C, an inhibitor of the adenosine monophosphate-activated protein kinase (AMPK) signaling (Lee et al. 2015; Lee et al. 2016). This finding suggested that MOTS-c-induced improvement of metabolic homeostasis in the mouse model of obesity may be mediated, at least in part, by AMPK signaling (Lee et al. 2015).

Although the molecular mechanisms by which MOTS-c increases AMPK signaling remain poorly understood, in-vitro experiments carried out in HEK-293 cells have shown that MOTS-c (10 μM, up to 72-hour incubation) downregulates enzymes involved in the one-carbon metabolic pathways, which include the folate and methionine cycles (Lee et al. 2015). As illustrated in Figure 7 by reducing the activity of the one-carbon metabolic pathways and decreasing the de-novo synthesis of purines, MOTS-c can cause accumulation of the intermediate 5-aminoimidazole-4-carboxamide (AICAR), which is a well-known AMPK activator, that can, in turn stimulate mitochondrial metabolism, fatty acid oxidation, glycolysis, and shunting of glucose to the glucose phosphate pathway.

Figure 7. Diagrammatic Representation of MOTS-c-Induced Regulation of Metabolic Homeostasis in Skeletal Muscles (Adapted From Lee et al. 2015).



Proposed mechanism of action: MOTS-c downregulates enzymes involved in the de-novo purine biosynthesis pathway, thereby inhibiting the pathway and causing accumulation of the de-novo purine synthesis intermediate AICAR, which, via AMPK activation, stimulates fatty acid oxidation, glycolysis, and shunting of glucose to the pentose phosphate pathway (PPP).
[-: inhibition; ⇧: increased activity; +: stimulation]

MOTS-c on Bone Remodeling

An in-vitro study demonstrated that MOTS-c can promote osteogenesis, i.e., the development of bone cells (Hu and Chen 2018). In this study, rat BMSCs were subjected to in-vitro osteogenic differentiation for 7 days in the absence or in the continuous presence of 1 μM MOTS-c (the highest MOTS-c concentration that had no significant effect on BMSC proliferation). The MOTS-c treatment of cultured BMSCs increased the cellular expression of osteogenesis-related genes, including alkaline phosphatase (ALP), runt-related transcription factor 2 (RUNX2), and osteocalcin (also known as bone gamma-carboxyglutamic acid-containing protein or BGLAP). The MOTS-c treatment also increased the presence of calcified nodules, a marker of osteogenesis, in the cultured cells. The finding that the MOTS-c-induced osteogenesis was not observed in BMSC cultures with a null expression of the gene that encodes the transforming growth factor β (TGFβ) suggested that the osteogenic effect of MOTS-c depends, at least in part, on the TGFβ signaling pathway, whose stimulation is known to promote bone remodeling (Hu and Chen 2018).

In addition to inducing osteogenesis, MOTS-c can inhibit osteolysis, i.e., the breakdown of bone tissue (Yan et al. 2019). In an in-vivo experiment, bone loss induced by implantation of ultra-high molecular weight polyethylene (UHMWPE) particles in the calvaria (the uppermost part of the skull) of adult male C57/BL6 mice was markedly reduced by local injection of MOTS-c (1 mM, 150 μL) once a day for 7 days in the UHMWPE-implanted area. In MOTS-c-treated, UHMWPE-implanted mice, the reduced bone loss was accompanied by significantly reduced number of osteoclasts (cells that degrade bone) per bone perimeter and markedly reduced the surface area that was eroded. In the calvaria of MOTS-c-treated, UHMWPE-implanted mice, the reduced numbers of cells positive for the osteoclast differentiation factor receptor activator of nuclear factor-κB ligand (RANKL) was accompanied by increased numbers of cells positive for the osteoclastogenesis inhibitor ostoprotegerin (Yan et al. 2019). As discussed below, data from an in-vitro experiment provided evidence that the inhibitory effect of MOTS-c on osteoclastogenesis was due to MOTS-c-induced suppression of secretion of osteoclast differentiation factors from osteocytes (Yan et al. 2019).

In their in-vitro experiment, Yan and collaborators incubated primary cultures of mouse osteocytes with MOTS-c (10, 20, or 30 μM) for 12 h, at which time the culture supernatants were collected and applied to primary cultures of mouse bone marrow macrophages (BMMs) under conditions that would favor the macrophage differentiation into osteoclasts. Supernatants from MOTS-c-treated osteocytes were reported to significantly inhibited osteoclastogenesis, i.e., the differentiation of BMMs into osteoclasts. Inhibition of osteoclastogenesis was greatest in cultured BMMs incubated with supernatants from osteocytes that had been treated with the highest MOTS-c concentration (30 μM). Conversely, osteoclastogenesis occurred in cultured BMMs that were incubated with supernatants collected from primary cultures of osteocytes that had been treated with MOTS-c (30 μM) plus the AMPK inhibitor compound C. These findings led the authors to conclude that the anticlastogenic effect of MOTS-c is mediated, at least in part, by its ability to increase the release of anticlastogenic factors from osteocytes via an AMPK-dependent mechanism (Yan et al. 2019).

MOTS-c on Vascular Calcification and Myocardial Remodeling

Considering reports that AMPK signaling suppresses vascular calcification, i.e. the pathological accumulation of calcium deposits in the walls of blood vessels that is associated with different clinical conditions including obesity, Wei and collaborators investigated the effects of MOTS-c in a rat model of vascular calcification (Wei et al. 2020). In this model, male Sprague-Dawley rats that are exposed daily to nicotine (5 mg/kg/day, oral gavage) plus vitamin D3 (300,000 U/kg/day, intramuscular or IM) for 4 weeks present with decreased vascular tension, increased blood pressure, and increased calcium deposition in the aorta in addition to myocardial remodeling characterized by echocardiographic reductions of the internal diameter of the left ventricle at diastole and systole. Treatment of the rats with MOTS-c (5 mg/kg/day, IP) during the time they were being exposed to nicotine-plus-vitamin D3 significantly reduced the pathological changes in vascular tension, blood pressure, aortic calcium deposition, and myocardial remodeling (Wei et al. 2020).

The 4-week exposure of rats to vitamin D3-plus-nicotine also reduced the phosphorylation (and, therefore, the activity) of AMPK and upregulated the expression of angiotensin II type 1 receptors (AT1Rs) and endothelin β receptors (ETβRs) in the aorta (Wei et al. 2020). Treatment with MOTS-c prevented the reduction of levels of phosphorylated AMPK and the upregulation of AT1Rs and ETβRs. The authors concluded that MOTS-c, most likely via AMPK-dependent signaling mechanisms that may contribute to downregulation of AT1Rs and ETβRs, inhibits vascular calcification and myocardial remodeling (Wei et al. 2020).

The pleiotropic pharmacological effects of MOTS-c on lipid and glucose metabolism, bone remodeling, and vascular calcification have prompted interest of researchers on the potential therapeutic effectiveness of this peptide for management of different clinical conditions, including obesity and osteoporosis (reviewed in Lee et al. 2016; Monteiro et al. 2019). However, caution is warranted in interpreting the potential clinical relevance of the nonclinical pharmacological effects of MOTS-c. To date, nonclinical pharmacological studies of MOTS-c have been limited to in-vivo and in-vitro rodent models and have not evaluated the dose-response relationships for the effects of MOTS-c in vivo. In addition, although the pharmacological effects of MOTS-c appear to depend, at least in part, on AMPK signaling, the molecular target(s)

through which MOTS-c acts remains unknown. As such, it is difficult to predict which organs might be targeted and affected by MOTS-c.

b. Pharmacokinetics/Toxicokinetics

At the time of this evaluation, the nominator did not submit, and FDA did not identify in-vivo pharmacokinetic or toxicokinetic studies of MOTS-c.

The only pharmacokinetic-related study FDA identified in the biomedical literature was an in-vitro study assessing the metabolic degradation of MOTS-c in human whole blood that had been incubated with MOTS-c (5 µg/mL) at 37°C for 15 or 60 minutes (Knoop et al. 2019). Using high resolution mass spectrometry, the authors identified the peptides MOTS-$c_{(2–16)}$, MOTS-$c_{(3–16)}$, MOTS-$c_{(4–16)}$, and MOTS-$c_{(5–16)}$ in MOTSC-c-incubated human blood (Figure 8). The authors stated that in-vitro proteolytic hydrolysis of MOTS-c into the shorter peptides was rapid and did not require its long incubation with human blood (Knoop et al. 2019). It remains to be determined whether exogenous administration of MOTS-c to humans can generate pharmacologically active concentrations of the peptide over time.

Figure 8. Amino Acid Sequences of MOTS-c Metabolites in Human Blood Incubated With MOTS-c In Vitro (Sequences Excerpted From Knoop et al. 2019).

MOTS-c	Met – Arg – Trp – Gln – Glu – Met – Gly – Tyr – Ile – Phe – Tyr – Pro – Arg – Lys – Leu – Arg
MOTS-$c_{(2-16)}$	Arg – Trp – Gln – Glu – Met – Gly – Tyr – Ile – Phe – Tyr – Pro – Arg – Lys – Leu – Arg
MOTS-$c_{(3-16)}$	Trp – Gln – Glu – Met – Gly – Tyr – Ile – Phe – Tyr – Pro – Arg – Lys – Leu – Arg
MOTS-$c_{(4-16)}$	Gln – Glu – Met – Gly – Tyr – Ile – Phe – Tyr – Pro – Arg – Lys – Leu – Arg
MOTS-$c_{(5-16)}$	Glu – Met – Gly – Tyr – Ile – Phe – Tyr – Pro – Arg – Lys – Leu – Arg

Left to right: Amino acid sequences from the N- to the C-terminus of the peptides. Arg: arginine; Gln: glutamine; Glu: glutamic acid; Gly: glycine; Ile: isoleucine; Leu: leucine; Lys: lysine; Met: methionine; Phe: phenylalanine; Pro: proline; Trp: tryptophan; Tyr: tyrosine.

c. Acute Toxicity[30]

At the time of this evaluation, the nominator did not submit, and FDA did not identify acute toxicity studies of MOTS-c (free base) or MOTS-c acetate.

[30] Acute toxicity refers to adverse effects observed following administration of a single dose of a substance, or multiple doses given within a short period (approximately 24 hours). For more information on general approaches for acute toxicity studies, please refer to FDA's guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), available at https://www.fda.gov/media/71542/download.

d. Repeat-Dose Toxicity[31]

At the time of this evaluation, the nominator did not submit, and FDA did not identify repeat-dose toxicity studies of MOTS-c (free base) or MOTS-c acetate.

e. Genotoxicity[32]

At the time of this evaluation, the nominator did not submit, and FDA did not identify genotoxicity studies of MOTS-c (free base) or MOTS-c acetate.

f. Developmental and Reproductive Toxicity[33]

At the time of this evaluation, the nominator did not submit, and FDA did not identify nonclinical developmental and reproductive studies of MOTS-c (free base) or MOTS-c acetate.

g. Carcinogenicity[34]

At the time of this evaluation, the nominator did not submit, and FDA did not identify nonclinical carcinogenicity studies of MOTS-c (free base) or MOTS-c acetate.

Conclusions: From the pharmacological perspective, nonclinical pharmacological studies submitted by the nominator and identified by FDA indicate that, in rodent models, MOTS-c, acting via AMPK-dependent mechanisms, can according to the authors: (i) improve glucose and

---

[31] Repeat-dose toxicity studies consist of in-vivo animal studies that seek to evaluate the toxicity of the test substance when it is repetitively administered daily for an extended period. For more information on general approaches for repeat-dose toxicity studies, please refer to FDA's guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), available at https://www.fda.gov/media/71542/download.

[32] The genotoxicity assessment battery usually consists of a gene mutagenicity assay (for single dose trials) and a variety of clastogenicity/genotoxicity assays. To support multiple dose administration in humans, additional genotoxicity testing assessment is usually conducted to detect chromosomal damage in mammalian systems. For more information on general approaches for genotoxicity studies, please refer to FDA's guidance for industry *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use* (June 2012), available at https://www.fda.gov/media/71980/download.

[33] Developmental and reproductive toxicity studies are usually designed to assess the potential adverse effects of a substance within a complete reproductive cycle, from conception to reproductive capacity in subsequent generations, and to identify the potential effects of a substance on pre-, peri-, and postnatal development. Developmental toxicity or teratogenicity refers to adverse effects (can include embryo-fetal mortality, structural abnormalities, functional impairment, or alterations to growth) and can occur in pups either as a result of the exposure of their parents to the substance, prior to the pups' birth, or by direct exposure of the pups to the substance after birth. For more information on general approaches for reproductive and developmental toxicity studies, please refer to FDA's guidance for industry *S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals* (May 2021), available at https://www.fda.gov/media/148475/download.

[34] Studies that assess cancer risk in animals are used as predictive tools to evaluate the potential for drugs to cause tumors when used by humans on a chronic basis. Carcinogenicity studies are conducted if the clinical use is expected to be continuous for a minimum of 6 months of life, or if intermittent clinical use is expected to total 6 months or more of life. For more information on general approaches for carcinogenicity studies, please refer to FDA's guidance for industry *S1B Testing for Carcinogenicity of Pharmaceuticals* (July 1997), available at https://www.fda.gov/media/71935/download.

lipid metabolism, (ii) increase osteogenesis and suppress osteolysis, and (iii) suppress vascular calcification and associated myocardial remodeling. These nonclinical findings sparked interest of researchers on the potential usefulness of MOTS-c as a pharmacological intervention for different clinical conditions, including obesity and osteoporosis. However, the findings should be interpreted with caution because the nonclinical pharmacological studies of MOTS-c published to date have been restricted to rodent models and have not assessed dose-response relationships for the different pharmacological effects of MOTS-c in vivo. In addition, while AMPK-dependent signaling appears to contribute to the pharmacological effects of MOTS-c, the molecular targets underlying the pharmacological effects of MOTS-c remain unknown making it difficult to predict which organs are likely to be affected by MOTS-c.

Although the nominator did not submit, and FDA did not identify in-vivo studies assessing the pharmacokinetic profile of MOTS-c, FDA identified an in-vitro study reporting that MOTS-c is quickly hydrolyzed in human blood. This finding raises the question as to whether exogenous administration of MOTS-c to humans can generate pharmacologically active concentrations of the peptide over time. At the time of this evaluation, the nominator did not submit, and FDA did not identify nonclinical toxicity studies to inform safety considerations for potential clinical uses of MOTS-c (free base) or MOTS-c acetate.

2. Human Safety

The following databases were consulted in the preparation of this section: PubMed, Embase, Cochrane Database of Systematic Reviews, FDA Adverse Event Reporting System (FAERS), ClinicalTrials.gov, professional healthcare organization websites, and various online clinical references and websites. Note that throughout this section, the substance will be generally referred to as MOTS-c unless otherwise specified as free base or acetate salt.

The nomination did not include, and FDA did not identify, information including human exposure data to evaluate whether MOTS-c-related BDSs are safe for use in compounded products.

a. Pharmacokinetic Data

The nominator did not submit, and FDA did not identify clinical studies that provided pharmacokinetic data for MOTS-c-related BDSs.

b. Reported Adverse Reactions

The Office of Surveillance and Epidemiology conducted searches of the FAERS database for reports of adverse events for MOTS-c through February 28, 2024, and from February 26, 2024 through March 9, 2025.[35] The searches retrieved no reports.

[35] Compounders under section 503A of the FD&C Act generally do not report adverse events to FDA. FDA encourages compounders, health care professionals, and consumers to report adverse events and product quality concerns associated with compounded drugs to FDA's MedWatch Adverse Event Reporting program. Unless an adverse event report is submitted to FDA, the Agency may not be aware of adverse events associated with a product compounded under section 503A.

c. Clinical Studies Assessing Safety

The nomination did not include, and FDA has not identified, any clinical studies or human exposure data for MOTS-c via any route of administration. Therefore, potential safety risks associated with the use of MOTS-c-related BDSs in humans are unknown.

d. Other Safety Information

Immunogenicity and Aggregation Concerns

FDA has issued guidance regarding immunogenicity assessment for therapeutic protein products.[36] The guidance describes immunogenicity as the propensity of a therapeutic protein product to generate immune responses to itself and to related proteins including endogenous proteins or peptides, or to induce immunologically related adverse clinical events. Although this guidance addresses therapeutic protein products, the concerns about immunogenicity are also relevant to peptides (such as MOTS-c), which can similarly elicit an immunogenic response; this immunogenic response may be enhanced when peptides are given via SC route of administration (ROA). In general, SC ROA is associated with increased immunogenicity compared to intravenous (IV) ROA.

The consequences of triggering an immune response may range from antibody responses with no apparent clinical manifestations to life-threatening and catastrophic reactions. Such outcomes are often unpredictable in patients administered therapeutic protein or peptide products. One possible consequence of the development of an immune response is the development of neutralizing antibody activity that may lead to loss of efficacy or even result in the neutralization of the activity of the endogenous peptide counterpart.

In addition, compared to small molecule active pharmaceutical ingredients, peptides are distinct because they may have an inherent tendency to aggregate. Aggregation refers to the processes through which peptides associate into larger species consisting of multiple peptide chains. Aggregates can be highly ordered or amorphous and the formation can be reversible or irreversible (Zapadka et al. 2017). Peptides with as few as two amino acids have been shown to aggregate (Frederix et al. 2011). Aggregates can impact the pharmacology of the peptide. In addition, aggregation is a risk factor in immunogenicity and for decreased pharmacotherapeutic effect of the drug product due to effects on bioavailability, formation of precipitates, or anti-drug antibody production (Ratanji et al. 2014).

The nominators did not provide, and FDA did not identify, clinical studies assessing immunogenicity or aggregation of MOTS-c-related BDSs. MOTS-c-related BDSs contains 16 amino acids, and FDA is concerned about potential for immunogenicity when administered by an injection ROA as proposed, due to the potential for aggregation, as well as potential peptide-related impurities. Based on available information, there are insufficient data to conclude that MOTS-c-related BDSs do not present these risks.

[36] See FDA's guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014), available at https://www.fda.gov/media/85017/download.

e. Therapies That Have Been Used for the Condition(s) Under Consideration

There are FDA-approved drug products for weight reduction in patients with obesity and treatment of osteoporosis.[37]

Conclusions: There is a lack of clinical and nonclinical safety information on the use of MOTS-c. FDA is particularly concerned about the lack of human data on drug products containing this substance administered via any route of administration. MOTS-c is a peptide containing 16 amino acids for which there is a lack of information to assess its immunogenic safety risk. Therefore, potential safety risks associated with the use of MOTS-c in humans are unknown. There are currently available FDA-approved therapies for some of the nominated uses.

D. Available Evidence of Effectiveness or Lack of Effectiveness of Drug Products Compounded With the Substance

The following databases were consulted in the preparation of this section: PubMed, Embase, Cochrane Database of Systematic Reviews, DailyMed, Drugs@FDA, relevant professional healthcare organization websites, and various online clinical references and websites, such as information from the Centers for Disease Control and Prevention (CDC).

MOTS-c-related BDSs were nominated for the following uses: insulin resistance, obesity,[38] osteoporosis,[39] vascular calcification, muscle/fat metabolism, and longevity. The nomination cited 12 literature references in support of the nomination; these did not include clinical studies.

---

[37] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the safety criterion, to the extent there may be therapies that have been demonstrated to be safe under the conditions of use set forth in the approved labeling. See 84 FR 4696.

[38] Obesity is defined by the increase in size and amount of fat cells in the body. Obesity is a chronic health condition that increases the risk for heart disease and is linked to other health problems, such as type 2 diabetes and cancer. Diagnosis may be based on medical history and high body mass index (BMI). For adults, obesity is defined as BMI ≥ 30 kg/m2. Treatment options may involve dietary or nutritional counselling, behavioral weight-loss programs, medicines, or surgery (See: Overweight and Obesity, NIH National Heart, Lung, and Blood Institute, accessed 8/23/2024, https://www.nhlbi.nih.gov/health/overweight-and-obesity).

[39] Osteoporosis is a bone disease that develops when bone mineral density (BMD) and bone mass decreases or when the structure and strength of bone changes; this can lead to a decrease in bone strength that can increase the risk of fractures. Osteoporosis is typically asymptomatic until fractures occur. Treatment of osteoporosis aims to prevent fractures and may include nutrition, exercise, and medications (See: Osteoporosis. NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases, accessed 3/20/2025, https://www.niams.nih.gov/health-topics/osteoporosis)

We performed our own search of published medical literature and did not identify clinical studies evaluating administration of MOTS-c-related BDSs in human subjects.[40]

1. *Reports of Trials, Clinical Evidence, and Anecdotal Reports of Effectiveness, or Lack of Effectiveness, of the Bulk Drug Substance*

We reviewed information from the nominator-cited references. The nominator has not provided clinical evidence on the use of MOTS-c-related BDSs in insulin resistance, obesity, osteoporosis, vascular calcification, muscle/fat metabolism, and longevity. We performed our own search of published medical literature, and we did not identify data, such as clinical studies, evaluating the administration of MOTS-c to humans.

2. *Whether the Product Compounded With This Bulk Drug Substance Is Intended To Be Used in a Serious or Life-Threatening Disease*

Patients with obesity are at increased risk for many serious diseases and health conditions such as type 2 diabetes, heart disease, stroke, and certain types of cancers.[41]

Osteoporosis is associated with increased risk of potentially serious fractures which can generate a heavy burden of morbidity and an increased risk of mortality (Leboime et al. 2010).

3. *Therapies That Have Been Used for the Condition(s) Under Consideration*

There are FDA-approved drug products for weight reduction in patients with obesity and treatment of osteoporosis.[42]

Conclusion: There is a lack of evidence to evaluate the effectiveness of the MOTS-c-related BDSs for the nominated uses. As discussed in section II.C.1, although nonclinical pharmacological studies investigated the role of MOTS-c on biological processes that could be relevant to the nominated uses, these studies were limited to in-vitro and in-vivo rodent models. In addition, assessments of the dose-response relationships for the effects of MOTS-c are missing, and the molecular target(s) through which MOTS-c acts remains unknown. It is difficult to predict which organs might be targeted and affected by MOTS-c. Therefore, the clinical relevance of the findings of these nonclinical studies is currently unknown. The nomination did not include, and our evaluation did not identify, information on the use of MOTS-c-related BDSs administered in humans in order to evaluate whether MOTS-c-related BDSs are appropriate for the proposed uses in compounded drug products. Obesity and osteoporosis are serious conditions

---

[40] FDA did not evaluate the proposed uses: insulin resistance, obesity, osteoporosis, vascular calcification, muscle/fat metabolism, longevity because the nomination did not include sufficient information for the Agency to evaluate whether the substance is appropriate for these uses in compounded drug products. In addition, FDA did not identify clinical studies evaluating these uses of MOTS-c. See 80 FR 65765 for the information necessary to fully evaluate a substance for inclusion on the 503A Bulks List.

[41] See: How Overweight and Obesity Impacts Your Health, CDC website, https://www.cdc.gov/healthy-weight-growth/food-activity/overweight-obesity-impacts-health.html. Accessed 8/23/2024.

[42] FDA considers the existence of FDA-approved or OTC monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.

and there are FDA-approved therapies for weight reduction in patients with obesity and treatment of osteoporosis.

III. CONCLUSION AND RECOMMENDATION

We have balanced the criteria described in section II above to evaluate MOTS-c related BDSs for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs against*** MOTS-c free base or MOTS-c acetate being placed on that list based on the following:

1. Conclusions on the physical and chemical characterization for each MOTS-c related BDS, MOTS-c (free base) and MOTS-c acetate, are included in subsections 1.1 and 1.2.

   1.1.

   MOTS-c (free base) is reported to be a peptide consisting of 16 amino acids. As reported in the literature, lyophilized MOTS-c (free base) is expected to be stable when stored below -20°C desiccated and protected from light.

   MOTS-c (free base) is considered to be not well-characterized from the physical and chemical characterization perspective because (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., INN, IUPAC, USAN), and (2) BDS specific quality control attributes, including impurities, aggregates, and endotoxins, were not found in the publicly available scientific literature and lack of CoA in the nomination package which are offered as evidence to establishing identity, purity, and impurity profiles of the substance. Due to lack of information on the water solubility data of MOTS-c (free base) as well as the reconstitute concentration of proposed injectable final product, it is difficult to draw a conclusion if the water solubility of MOTS-c (free base) will be a potential issue to impact product performance for the proposed injectable dosage form. In addition, due to lack of information regarding potential peptide related impurities and potential of peptide aggregates that can be present in MOTS-c (free base) FDA cannot rule out the potential for immunogenicity associated with them, especially when administered by injection routes.

   1.2.

   MOTS-c acetate is reported to be an acetate salt of peptide consisting of 16 amino acids. As reported in the literature, MOTS-c acetate is expected to be stable under reported storage conditions (below -20°C).

   MOTS-c acetate is considered not well-characterized from the physical and chemical characterization perspective because (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., INN, IUPAC, USAN), and (2) certain critical characterization data specific to MOTS-c acetate (including impurities, aggregates, and microbial bioburden and/or bacterial endotoxin levels) were not found in the publicly available scientific literature, and the provided CoA, which was offered as evidence to establishing identity, purity, and impurity profiles of the substance. We cannot evaluate how the water solubility of MOTS-c acetate will impact the performance of the proposed

injectable final product due to lack of information on how to compound the proposed injectable product with known concentration. In addition, due to lack of information regarding potential peptide related impurities and potential of peptide aggregates that can be present in MOTS-c acetate FDA cannot rule out the potential for immunogenicity associated with them, especially when administered by injection routes.

2. MOTS-c was discovered in 2015. A search of published literature did not reveal studies in which compounded drug products containing MOTS-c or MOTS-c acetate were used in humans. OFs have not reported preparing single or multiple API compounded drug products containing MOTS-c or MOTS-c acetate. Internet search results indicate that injectable MOTS-c is marketed for different uses, including regulating mitochondrial energy, promoting the metabolism of fatty acid in the liver; promoting metabolic homeostasis; improving glucose regulation; aiding in the resistance of metabolic stress; protecting against insulin resistance; promoting weight loss, and improving physical performance. MOTS-c and MOTS-c acetate do not have an applicable USP or NF drug substance monograph and neither is a component of an FDA-approved drug. MOTS-c is listed as a prohibited substance in the Global DRO Database, which obtains information from the 2024 World-Anti-Doping Agency Prohibited List of Hormone and Metabolic Modulators.

3. There is a lack of evidence to evaluate the effectiveness of the MOTS-c-related BDSs for the nominated uses. Although nonclinical pharmacological studies investigated the role of MOTS-c on biological processes that could be relevant to the nominated uses, these studies were limited to in-vitro and in-vivo rodent models. In addition, assessments of the dose-response relationships for the effects of MOTS-c are missing, and the molecular targets through which MOTS-c acts remain unknown. It is difficult to predict which organs might be targeted and affected by MOTS-c. Therefore, the clinical relevance of the findings of these nonclinical studies is currently unknown. The nomination did not include, and our evaluation did not identify, information on the use of MOTS-c-related BDSs administered in humans in order to evaluate whether MOTS-c-related BDSs are appropriate for the proposed uses in compounded drug products. Obesity and osteoporosis are serious conditions and there are FDA-approved therapies for weight reduction in patients with obesity and treatment of osteoporosis.

4. There is a lack of clinical and nonclinical information on MOTS-c-related BDSs. FDA is particularly concerned about the lack of human data on drug products containing this substance delivered via any route of administration. MOTS-c is a peptide containing 16 amino acids for which there is a lack of information to assess its immunogenic safety risk. Therefore, potential safety risks associated with the use of MOTS-c-related BDSs in humans are unknown. There are currently available FDA-approved therapies for some of the nominated uses.

On balance, the physicochemical characterization, information on historical use, lack of any safety and effectiveness information in humans for both MOTS-c (free base) and MOTS-c acetate weigh against their being added to the 503A Bulks List. FDA's proposal is based on the fact that these substances are not well-characterized from a physical and chemical characterization perspective, unknown use in compounding, no available nonclinical data to inform safety considerations for potential clinical uses of MOTS-c-related BDSs, and no clinical

studies to assess the safety and effectiveness of MOTS-c-related BDSs in humans. Accordingly, we propose not adding MOTS-c (free base) or MOTS-c acetate to the 503A Bulks List.

IV. REFERENCES

Bhullar, KS, N Shang, E Kerek, K Wu and J Wu, 2021, Mitofusion Is Required for MOTS-c Induced GLUT4 Translocation, Sci Rep, 11(1):14291.

Frederix, PW, RV Ulijn, NT Hunt and T Tuttle, 2011, Virtual Screening for Dipeptide Aggregation: Toward Predictive Tools for Peptide Self-Assembly, J Phys Chem Lett, 2(19):2380-2384.

Fuku, N, H Pareja-Galeano, H Zempo, R Alis, Y Arai, A Lucia and N Hirose, 2015, The Mitochondrial-Derived Peptide MOTS-C: A Player in Exceptional Longevity?, Aging Cell, 14(6):921-923.

Hu, BT and WZ Chen, 2018, Mots-C Improves Osteoporosis by Promoting Osteogenic Differentiation of Bone Marrow Mesenchymal Stem Cells Via TGF-β/Smad Pathway, Eur Rev Med Pharmacol Sci, 22(21):7156-7163.

Kim, SJ, B Miller, HH Mehta, J Xiao, J Wan, TE Arpawong, K Yen and P Cohen, 2019, The Mitochondrial-Derived Peptide MOTS-c Is a Regulator of Plasma Metabolites and Enhances Insulin Sensitivity, Physiol Rep, 7(13):e14171.

Knoop, A, A Thomas and M Thevis, 2019, Development of a Mass Spectrometry Based Detection Method for the Mitochondrion-Derived Peptide MOTS-c in Plasma Samples for Doping Control Purposes, Rap Comm Mass Spec, 33(4):371-380.

Leboime, A, C Confavreux, N Mehsen, J Paccou, C David and C Roux, 2010, Osteoporosis and Mortality, Joint Bone Spine, 77(S2): S107-S112.

Lee, C, KH Kim and P Cohen, 2016, MOTS-c: A Novel Mitochondrial-Derived Peptide Regulating Muscle and Fat Metabolism, Free Radic Biol Med, 100:182-187.

Lee, C, J Zeng, BG Drew, T Sallam, A Martin-Montalvo, J Wan, S-J Kim, H Mehta, AL Hevener and R de Cabo, 2015, The Mitochondrial-Derived Peptide MOTS-c Promotes Metabolic Homeostasis and Reduces Obesity and Insulin Resistance, Cell Metab, 21(3):443-454.

Lu, H, S Tang, C Xue, Y Liu, J Wang, W Zhang, W Luo and J Chen, 2019a, Mitochondrial-Derived Peptide MOTS-c Increases Adipose Thermogenic Activation to Promote Cold Adaptation, Int J Mol Sci, 20(10):2456.

Lu, H, M Wei, Y Zhai, Q Li, Z Ye, L Wang, W Luo, J Chen and Z Lu, 2019b, MOTS-C Peptide Regulates Adipose Homeostasis to Prevent Ovariectomy-Induced Metabolic Dysfunction, J Mol Med (Berl), 97(4):473-485.

Monteiro, A, G Scarlato, DF Cavalini and GE Shiguemoto, 2019, Humanin, MOTS-c and Physical Exercise: A New Perspective, Biomed Res, 3:1-6.

Ratanji, KD, JP Derrick, RJ Dearman and I Kimber, 2014, Immunogenicity of Therapeutic Proteins: Influence of Aggregation, J Immunotoxicol, 11(2):99-109.

Reynolds, JC, RW Lai, JS Woodhead, JH Joly, CJ Mitchell, D Cameron-Smith, R Lu, P Cohen, NA Graham and BA Benayoun, 2021, MOTS-c Is an Exercise-Induced Mitochondrial-Encoded Regulator of Age-Dependent Physical Decline and Muscle Homeostasis, Nat Commun, 12(1):1-11.

Wei, M, L Gan, Z Liu, L Liu, J-R Chang, D-C Yin, H-L Cao, X-L Su and WW Smith, 2020, Mitochondrial-Derived Peptide MOTS-c Attenuates Vascular Calcification and Secondary Myocardial Remodeling Via Adenosine Monophosphate-Activated Protein Kinase Signaling Pathway, Cardiorenal Med, 10(1):42-50.

Yan, Z, S Zhu, H Wang, L Wang, T Du, Z Ye, D Zhai, Z Zhu, X Tian and Z Lu, 2019, MOTS-c Inhibits Osteolysis in the Mouse Calvaria by Affecting Osteocyte-Osteoclast Crosstalk and Inhibiting Inflammation, Pharmacol Res, 147:104381.

Yang, Y, H Gao, H Zhou, Q Liu, Z Qi, Y Zhang and J Zhang, 2019, The Role of Mitochondria-Derived Peptides in Cardiovascular Disease: Recent Updates, Biomed Pharmacother, 117:109075.

Zapadka, KL, FJ Becher, AL Gomes Dos Santos and SE Jackson, 2017, Factors Affecting the Physical Stability (Aggregation) of Peptide Therapeutics, Interface Focus, 7(6):20170030.

Zheng, Y, Z Wei and T Wang, 2023, MOTS-c: A promising mitochondrial-derived peptide for therapeutic exploitation. Front Endocrinol (Lausanne), 14:1120533.

V. APPENDICES

APPENDIX 1: AFFIRM HEALTH CENTER MOTS-c WEBPAGE (ACCESSED 3/20/24)

In this second blog, let's discuss our other Accelerated Fitness Program. It is our Short-Term Fitness Program, and it requires only a one-month commitment. The Short-Term Fitness Program includes the MOTS-c peptide in conjunction with nutritional guidance to accelerate weight loss, specifically the breakdown of fat. We use the MOTS-c peptide for this program as it delivers faster results than the AOD-9604 peptide we use for our three-month program.

What Is The MOTS-C Peptide?

MOTS-c is a mitochondrial-derived peptide described as a bioactive 16 amino acid peptide. This peptide is detected in circulation, so it is classified as a mitochondrial or metabolic hormone. It primarily targets fat and skeletal muscle. This makes MOTS-c a perfect addition to our Accelerated Fitness Program at Affirm.

What Are The Benefits Of The MOTS-C Peptide?

Research done on this peptide has shown beneficial effects in reducing diabetes and obesity while also enhancing performance and longevity. Why does this happen? MOTS-c assists proper mitochondrial function, and the mitochondria are the energy center of every cell in the human body. Research has shown that MOTS-c is an exercise-mimetic peptide, meaning it makes the body think it is exercising even when it is not.

These are the benefits of MOTS-c:

- Regulates mitochondrial energy
- Promotes the metabolism of fatty acid in the liver
- Promotes metabolic homeostasis
- Improves glucose regulation

https://web.archive.org/web/20251110203022/https://affirmhealthcenter.com/our-short-term-fitness-program-and-the-mots-c-peptide/

- Aids in the resistance of metabolic stress
- Protects against insulin resistance
- Promotes weight loss
- Improves physical performance

How Does The MOTS-C Peptide Boost Metabolism?

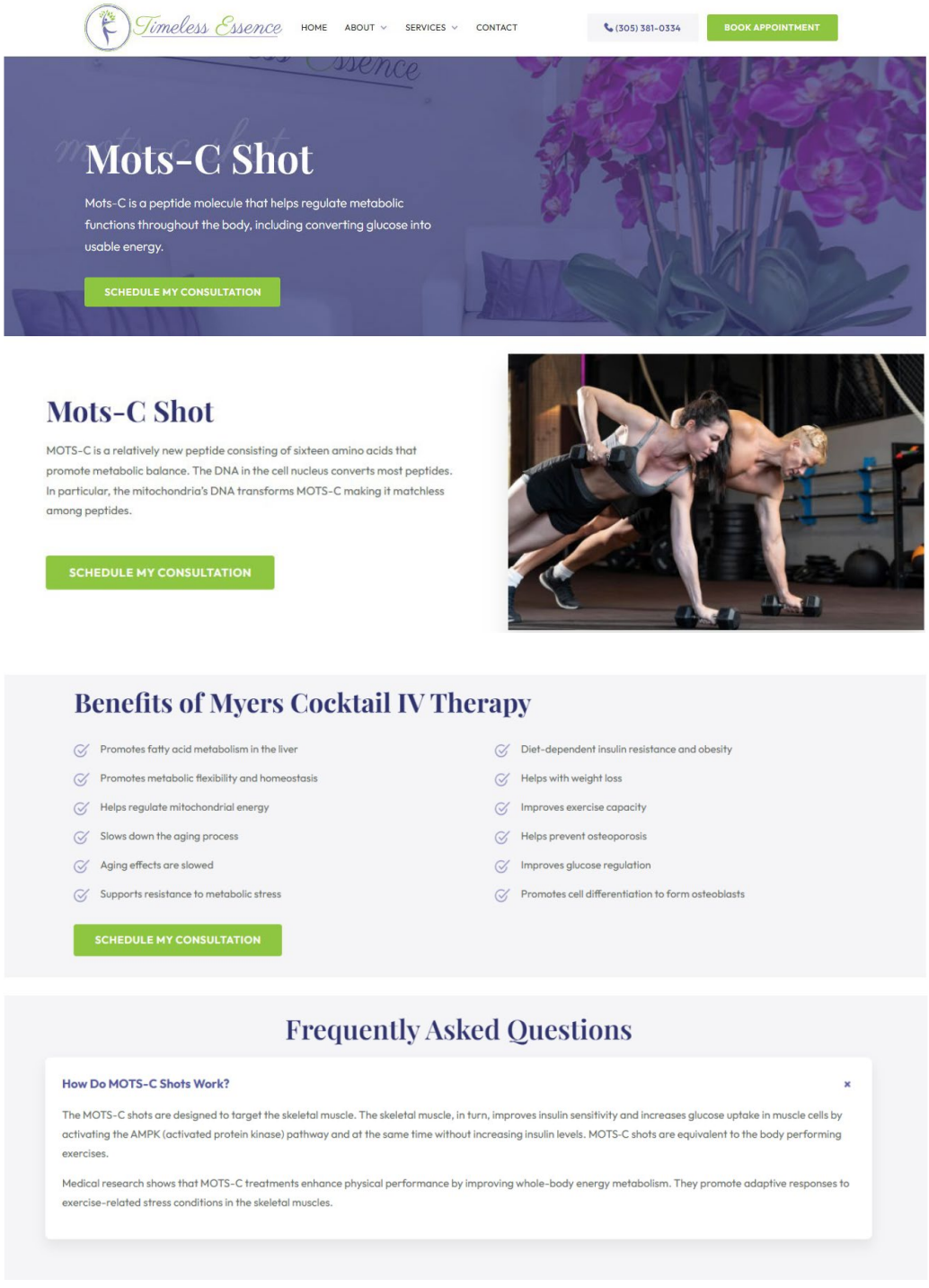
Functional metabolism is fueled by adequate glucose and insulin regulation, optimal mitochondrial function, and proper energy usage. Insulin production regulates whether or not the body uses glucose as energy or stores it as fat. Research indicates that the mitochondria are actively involved in metabolic homeostasis at the cellular level. MOTS-c works to reduce insulin resistance, helping the body use carbohydrates more efficiently.

Do you need help trying to achieve your weight-loss goals? Call us at Affirm Health Center, (417) 823-3901, and ask about our Accelerated Fitness Programs.

← Previous Post

Next Post →

APPENDIX 2: MYERS COCKTAIL IV THERAPY WEBPAGE (ACCESSED 3/20/24)



MOTS-c – Related Bulk Drug Substances (MOTS-c (free base) and MOTS-c acetate) Nomination

Company Name	**Wells Pharmacy Network**
Contact Name	**Anthony Campbell, PharmD, BCSCP**
Contact Phone	**352-622-2913**
Contact Email	**ACampbell@wellsrx.com**

503A Bulk Drug Substance Nomination	
What is the name of the nominated ingredient?	Mitochondrial Open Reading Frame of the 12S rRNA-c (MOTs-C)
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in 207.3 (a)(4)? ***Active ingredient*** means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.	YES
Is the ingredient listed in any of the three sections of the Orange Book?	NO
Were any drug monographs for the ingredient found in the USP or NF monographs?	NO
What is the chemical name of the substance?	Mitochondria-derived peptide mots-c <u>IUPAC Name:</u> (4*S*)-4-[[(2*S*)-5-amino-2-[[(2*S*)-2-[[(2*S*)-2-[[(2*S*)-2-amino-4-methylsulfanylbutanoyl]amino]-5-carbamimidamidopentanoyl]amino]-3-(1*H*-indol-3-yl)propanoyl]amino]-5-oxopentanoyl]amino]-5-[[(2*S*)-1-[[2-[[(2*S*)-1-[[(2*S*,3*S*)-1-[[(2*S*)-1-[[(2*S*)-1-[(2*S*)-2-[[(2*S*)-1-[[(2*S*)-6-amino-1-[[(2*S*)-1-[[(1*S*)-4-carbamimidamido-1-carboxybutyl]amino]-4-methyl-1-oxopentan-2-yl]amino]-1-oxohexan-2-yl]amino]-5-carbamimidamido-1-oxopentan-2-yl]carbamoyl]pyrrolidin-1-yl]-3-(4-hydroxyphenyl)-1-oxopropan-2-yl]amino]-1-oxo-3-phenylpropan-2-yl]amino]-3-methyl-1-oxopentan-2-yl]amino]-3-(4-hydroxyphenyl)-1-oxopropan-2-yl]amino]-2-oxoethyl]amino]-4-methylsulfanyl-1-oxobutan-2-yl]amino]-5-oxopentanoic acid $C_{101}H_{152}N_{28}O_{22}S_2$ <u>Amino Acid Sequence:</u> Met, Arg, Trp, Gln, Glu, Met, Gly, Tyr, Ile, Phe, Tyr, Pro, Arg, Lys, Leu, and Arg <u>CAS</u>: 1627580-64-6
What is the common name of the substance?	MOTs-C

Does the substance have a UNII code?	A5CV6JFB78
What is the chemical grade of the substance?	Provided by FDA Registered Supplier/COA
What is the strength, quality, stability, and purity of the ingredient?	Assay, Description, Solubility, etc.; Example of Certificate of Analysis for this chemical is attached.
How is the ingredient supplied?	Lyophilized Powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	No
Has information been submitted about the substance to the USP for consideration of drug monograph development?	No
What dosage form(s) will be compounded using the bulk drug substance?	Injectable
What strength(s) will be compounded from the nominated substance?	5mg and 10mg Lyophilized Vial
What is the anticipated route(s) of administration of the compounded drug product(s)?	Subcutaneous Injection
Are there safety and efficacy data on compounded drugs using the nominated substance?	Lee C, Zeng J, Drew BG, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. Cell Metab. 2015;21(3):443-454. doi:10.1016/j.cmet.2015.02.009 Lee C, Kim KH, Cohen P. MOTS-c: A novel mitochondrial-derived peptide regulating muscle and fat metabolism. *Free Radic Biol Med*. 2016;100:182-187. doi:10.1016/j.freeradbiomed.2016.05.015 Lu H, Wei M, Zhai Y, et al. MOTS-c peptide regulates adipose homeostasis to prevent ovariectomy-induced metabolic dysfunction. *J Mol Med (Berl)*. 2019;97(4):473-485. doi:10.1007/s00109-018-01738-w Kim SJ, Miller B, Mehta HH, et al. The mitochondrial-derived peptide MOTS-c is a regulator of plasma metabolites and enhances insulin sensitivity. *Physiol Rep*. 2019;7(13):e14171. doi:10.14814/phy2.14171 Crescenzo R, Bianco F, Mazzoli A, Giacco A, Liverini G, Iossa S. A possible link between hepatic mitochondrial dysfunction and diet-induced insulin resistance. *Eur J Nutr*. 2016;55(1):1-6. doi:10.1007/s00394-015-1073-0 Hu BT, Chen WZ. MOTS-c improves osteoporosis by promoting osteogenic differentiation of bone marrow mesenchymal stem cells via TGF-β/Smad pathway. *Eur Rev Med Pharmacol Sci*. 2018;22(21):7156-7163. doi:10.26355/eurrev_201811_16247 Fuku N, Pareja-Galeano H, Zempo H, et al. The mitochondrial-derived peptide MOTS-c: a player in exceptional longevity?. *Aging Cell*. 2015;14(6):921-923. doi:10.1111/acel.12389 Yang Y, Gao H, Zhou H, et al. The role of mitochondria-derived peptides in cardiovascular disease: Recent updates. *Biomed Pharmacother*. 2019;117:109075. doi:10.1016/j.biopha.2019.109075

Has the bulk drug substance been used previously to compound drug product(s)?	YES
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Insulin Resistance, Obesity, Osteoporosis, Vascular Calcification, Muscle/Fat Metabolism, Longevity
What is the reason for use of a compounded drug product rather than an FDA-approved product?	no FDA-approved product available
Is there any other relevant information?	Added as an Attachment

Certificate of Analysis

MOTs-C Acetate

Product Name : MOTs-C Acetate
Lot No. : DL5419
Mfg. Date : Jun 08, 2020
Exp. Date : Jun 07, 2023
CAS No. : 1627580-64-6
Batch Qty : 100g
Sequence : NH_2-Met-Arg-Trp-Gln-Glu-Met-Gly-Tyr-Ile-Phe-Tyr-Pro-Arg-Lys-Leu-Arg-COOH

TESTS	SPECIFICATIONS		RESULTS
Appearance	White to off-white powder		White powder
Solubility	Soluble in water		Conform
Amino Acid Composition	Met	1.8 – 2.2	2.0
	Ile	0.9 – 1.1	0.9
	Arg	2.7 – 3.3	3.1
	Phe	0.9 - 1.1	0.9
	Glx	1.8 - 2.2	2.0
	Pro	0.9 – 1.1	1.0
	Gly	0.9 – 1.1	1.0
	Lys	0.9 – 1.1	1.1
	Tyr	1.8 – 2.2	1.9
	Leu	0.9 – 1.1	1.1
Mass spectrum	2174.6±1.0		2174.3
Peptide purity (HPLC)	≥ 98.0%		99.2%
Acetic Acid (HPLC)	≤ 13.0%		9.1%
Water content (KF)	≤ 7.0%		4.7%
Peptide content (N%)	≥ 80.0%		85.6%
Conclusion: The product is a synthetic peptide and meets the specifications. Long Term Storage: Store in a sealed container at 2°C - 8°C in a Fridge or in a Freezer. Distributed by Darmerica.			

Note: Analytical results transcribed from the original COA provided by Hsinchen Yuan Biological Technology Co. Ltd.; Lot no. MOTs20200602

99.2% × 90.9% × 95.3% = 85.9% Δ

Based on the review of above information, the lot stands released.

	Name	Title	Signature	Date
Prepared by	Kamlesh Mistry	Quality Associate	K.R. Mistry	07/07/2020
Released by	Sai Rasane	Quality Assistant		07/16/2020

91.25

References included with nomination FDA-2015-N-3534-0293

Lu H, Tang S, Xue C, Liu Y, Wang J, Zhang W, Luo W, Chen J. Mitochondrial-Derived Peptide MOTS-c Increases Adipose Thermogenic Activation to Promote Cold Adaptation. Int J Mol Sci. 2019 May 17;20(10):2456. doi: 10.3390/ijms20102456. PMID: 31109005; PMCID: PMC6567243.

Monteiro A, Scarlato G, Cavalini D, Shiguemoto G. Humanin, MOTS-c and physical exercise: A new perspective. Biomedical Research and Reviews. Biomedical Research and Review. 2019. doi: 10.15761/brr.1000129.

Reynolds JC, Lai RW, Woodhead JST, Joly JH, Mitchell CJ, Cameron-Smith D, Lu R, Cohen P, Graham NA, Benayoun BA, Merry TL, Lee C. MOTS-c is an exercise-induced mitochondrial-encoded regulator of age-dependent physical decline and muscle homeostasis. Nat Commun. 2021 Jan 20;12(1):470. doi: 10.1038/s41467-020-20790-0. PMID: 33473109; PMCID: PMC7817689.

Wei M, Gan L, Liu Z, Liu L, Chang JR, Yin DC, Cao HL, Su XL, Smith WW. Mitochondrial-Derived Peptide MOTS-c Attenuates Vascular Calcification and Secondary Myocardial Remodeling via Adenosine Monophosphate-Activated Protein Kinase Signaling Pathway. Cardiorenal Med. 2020;10(1):42-50. doi: 10.1159/000503224. Epub 2019 Nov 6. PMID: 31694019.