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.

KPV–Related Bulk Drug Substances (KPV (Free Base) and KPV acetate)

Table of Contents

FDA Evaluation of KPV–Related Bulk Drug Substances (KPV (Free Base) and KPV acetate)

DATE: 5/12/2026

FROM: Jing Li, PhD
Pharmaceutical Scientist, Office of Product Quality Assessment II (OPQA II), Office of Pharmaceutical Quality (OPQ)

Nga-Lai Poon, PharmD
Regulatory Specialist, Office of Compounding Quality and Compliance (OCQC), Office of Compliance (OC)

Kemi Asante, PharmD, MPH, RAC
Lead Consumer Safety Officer, OCQC, OC

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

Andrea Benedict, PhD
Nonclinical Supervisor, DPT-RPURM/SM, OND

Emily Kneeream, PharmD
Clinical Analyst, Pharmacy Compounding Review Team (PCRT), Office of Specialty Medicine (OSM), OND

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

THROUGH: Russell Wesdyk, BS, MBA
Associate Director Regulatory Affairs, OPQA II, 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 KPV-related Bulk Drug Substances (KPV (free base) and KPV acetate) for Inclusion on the 503A Bulk Drug Substances List

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

List of Abbreviations

Abbreviation	Term
AE	adverse event
α-MSH	α-melanocyte-stimulating hormone
API	active pharmaceutical ingredient
BPC	Body Protection Compound
BDS	bulk drug substance
CAS	Chemical Abstracts Service
CDC	Centers for Disease Control and Prevention
CoA	Certificate of Analysis
FAERS	FDA Adverse Events Reporting System
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
HFCS	Human Foods Complaint Systems
INN	International Nonproprietary Names
IUPAC	International Union of Pure and Applied Chemistry
MF/MW	Molecular formula/ Molecular weight
KPV	lysine-proline-valine
NF	National Formulary
NIH	National Institutes of Health
OF	outsourcing facility
UNII	Unique Ingredient Identifier
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 KPV (lysine-proline-valine) 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 KPV-related BDSs provided inconsistent information in the nomination package regarding the specific BDS proposed. Specifically, it is unclear whether the nomination was for KPV (free base) or KPV acetate. KPV (free base) and KPV acetate are different active 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.

KPV is reported to be a tripeptide composed of the amino acids lysine (K), proline (P), and valine (V). Although it is unclear whether the nominator intended to nominate KPV (free base) or KPV acetate, FDA has decided to evaluate both on its own initiative.

KPV-related BDSs were evaluated for the following uses: wound healing and inflammatory conditions.[3] The KPV-related drug products proposed in the nominations are cream and gel, 0.1% for topical administration.

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

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

---

[1] The nomination of "KPV (lysine-proline-valine)" was from Wells Pharmacy Network (Document ID: FDA-2015-N-3534-0294) can be accessed at: https://www.regulations.gov/document/FDA-2015-N-3534-0294. The nomination was withdrawn, but because FDA is evaluating KPV (free base) and KPV 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.

II. EVALUATION CRITERIA

A. Is the Substance Well-Characterized, Physically and Chemically?[4]

KPV is a common name and not a United States Adopted Name (USAN).[5] 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[6], IUPAC[7], 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 KPV-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)[8] 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 moiety.[9] Different active moieties are not interchangeable because they can have different safety and efficacy profiles. A free base or the various salts or ester forms of an active moiety are

---

[4] 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).

[5] 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.

[6] 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.

[7] 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.

[8] The terms BDS and 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."

[9] "*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.

distinct APIs, 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.

For the purpose of this assessment, we will consider both KPV (free base) and KPV acetate and will evaluate the physical and chemical characterization of each. Table 1 below summarizes available identifying information obtained from public domain for each BDS.

Table 1. Summary of Basic Information on KPV (Free Base) and KPV Acetate.

Characteristic	KPV (Free Base)	KPV Acetate
UNII[10] Code	Not available	Not available
CAS No.	67727-97-3	The CAS number used is the same as KPV (free base)*
MF/MW (g/mol)	$C_{16}H_{30}N_4O_4$/342.43	$C_{16}H_{30}N_4O_4 \cdot CH_3COOH$/402.5[11,12]
Peptide Sequence	H-Lys-Pro-Val-OH	H-Lys-Pro-Val-OH ·CH_3COOH
Supplier[13]	Yes	Yes
Active Moiety	KPV (free base)	KPV (free base)

* CAS is an abbreviation of Chemical Abstracts Service. The CAS number for KPV acetate is the same as that for KPV (free base) in most public references (for more information, see the Echemi website for KPV, available at: https://www.echemi.com/produce/pr2305301691-kpv-peptide-alpha-msh-11-13-acetate-salt-98-white-powder-youngshe.html; and the JennysChem website for KPV, available at: https://jennyschem.com/lys-pro-val-nh2-kpv-acetate-salt-67727-97-3/). MF/MW: molecular formula/molecular weight; UNII: Unique Ingredient Identifier

One nomination was submitted, which, as discussed above, was later withdrawn. The nominator provided inconsistent information about the different KPV BDSs in their nomination package. Due to inconsistencies in the nomination, it is unclear which KPV-related BDS the nominator intended to nominate. For example, the certificate of analysis (CoA) submitted with the nomination refers to one BDS by name in the title and a different BDS by the molecular formula. All chemistry-related information about the BDSs provided by the nominator is summarized in Table 2.

[10] The Unique Ingredient Identifier (UNII) is an alphanumeric identifier linked to a substance's molecular structure or descriptive information and is generated by the Global Substance Registration System (GSRS) of the Food and Drug Administration (FDA).
[11] See the Echemi website for KPV, available at: https://www.echemi.com/produce/pr2305301691-kpv-peptide-alpha-msh-11-13-acetate-salt-98-white-powder-youngshe.html. Accessed April 03, 2025.
[12] See the JennysChem product page for KPV, available at: https://jennyschem.com/lys-pro-val-nh2-kpv-acetate-salt-67727-97-3/. Accessed April 03, 2025.
[13] 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 certificates of analysis (COAs) associated with their production, which can help FDA to identify and characterize BDSs.

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

Nominator	1
Nominated BDS	KPV
BDS per UNII Code	Not available
CoA	CoA provided for KPV Acetate
CAS No.	67727-97-3 *(matches KPV free base)*
MF	$C_{16}H_{30}N_4O_4$ *(provided in the nomination package/CoA that matches KPV free base)*
MW (g/mol)	Not provided
Chemical Name	(2S)-2-[[(2S)-1-[(2S)-2,6-diaminohexanoyl]pyrrolidine-2-carbonyl]amino]-3-methylbutanoic acid *(matches KPV free base)*

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

Due to FDA's significant safety concerns related to this nomination/BDS, FDA is choosing to concurrently evaluate both BDSs (KPV (free base) and KPV acetate) in this section under two different subsections (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:

- Cream/Gel with the Strength of 0.1% for Topical Use

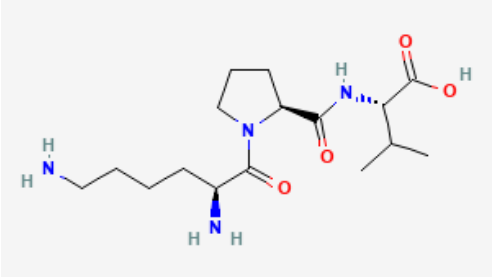
There is no USP drug substance monograph for KPV (free base) or its acetate salt. We reviewed physical and chemical characterization-related information provided by the nominator and performed a literature search for additional information on KPV (free base) and its acetate, especially those that may impact the performance for the proposed cream/gel dosage forms. Databases searched for information on KPV (free base) and its acetate in preparation of this section included SciFinder, Analytical Profiles of Drug Substances, PubMed, the European Pharmacopoeia, and the USP-NF.

1. KPV (Free Base)

KPV is reported to be a tripeptide composed of the amino acids lysine (K), proline (P), and valine (V). It is naturally produced in the body and is a fragment derived from the neuropeptide produced in the pituitary gland called α-melanocyte-stimulating hormone (α-MSH)[14]. The molecular formula of KPV (free base) is $C_{16}H_{30}N_4O_4$ and its molecular weight is 342.43 g/mol. Its chemical structure is shown in Figure 1. There is no CoA for KPV (free base) in the nomination.

[14] See the MindBodyFunctionalMedicine website for KPV, available at: https://mindbodyfunctionalmedicine.com/blog/peptide-therapy-kpv-the-anti-inflammation-pro-healing-peptide/. Accessed August 26, 2024.

Figure 1. The Chemical Structure of KPV (Free Base).[15]



a. Stability of the API and Likely Dosage Forms

It is reported that lyophilized KPV (free base) is stable up to 3 years when stored at -20°C in a tightly closed container, up to 2 years at 4°C, and up to 3 months at 15°C. Upon reconstitution, reports indicate the aqueous solution is recommended to be stored at -80°C for 6 months, at -2°C for 1 month, and 10°C for 1 week.[16]

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.

b. Probable Routes of API Synthesis

KPV was reported to be synthesized via the following four steps:

1. Using a polymer-bonded polyoxyethylene-RAM (Rink Amide linker) resin as a synthetic solid phase substrate and pretreating it.
2. Adding N-fluorenylmethoxycarbonyl-AA-OH and a polypeptide linking reagent to the resin for amino acid synthesis, washing the resin, and removing N- protected with methoxycarbonyl, cleaning the resin again.

[15] See the Peptide Sciences website for KPV 5 mg, available at: https://www.peptidesciences.com/kpv-5mg. Accessed April 10, 2025.
[16] See the CoA for KPV 2 mg, available at: https://www.uk-peptides.com/image/catalog/COA/COA%20PEPTIDES%20WEBSITE%2042.pdf. Accessed August 26, 2024.

3. The peptide chain obtained is carboxylated by acetic acid or dichloromethane to obtain a carboxylated peptide chain.
4. Cutting the peptide chain with trifluoroacetic acid, triisopropylsilane and water, washing same with methyl tributyl ether, and centrifuging same for precipitation, and drying the precipitate and purifying same using HPLC (high-performance liquid chromatography) to obtain KPV peptide.[17]

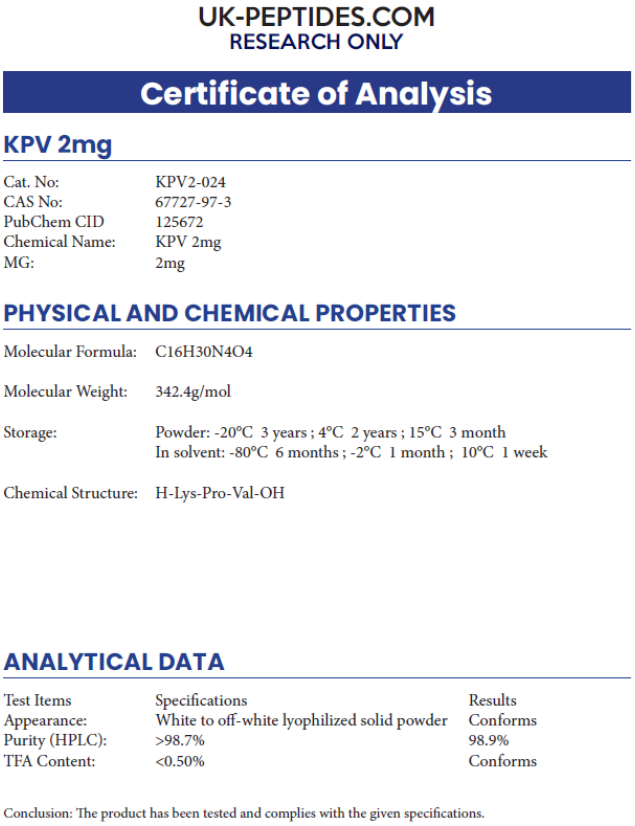
c. Likely Impurities[18]

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 KPV (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 KPV (free base) in the nomination. We conducted literature searches and found that most of CoA for KPV (free base) only contains purity testing result, as shown in the example CoA below (Figure 2).[19] 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 KPV (free base). In addition, there is lack of information on the potential of peptide aggregation for KPV (free base).

[17] See the patent for the preparation of KPV and analogs thereof, available at: https://patents.google.com/patent/WO2017107241A1/en. Accessed August 26, 2024.
[18] 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 in account the amount of the impurity, dose, route of administration, and chronicity of dosing. When 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 D.1. as part of the safety assessment of the substance.
[19] See the UK Peptides website for KPV 2 mg, available at: https://www.uk-peptides.com/kpv-2mg. Accessed August 26, 2024.

Figure 2. Example of a Certificate of Analysis for KPV (Free Base).



UK-PEPTIDES.COM
RESEARCH ONLY

Certificate of Analysis

KPV 2mg

Cat. No:	KPV2-024
CAS No:	67727-97-3
PubChem CID	125672
Chemical Name:	KPV 2mg
MG:	2mg

PHYSICAL AND CHEMICAL PROPERTIES

Molecular Formula:	C16H30N4O4
Molecular Weight:	342.4g/mol
Storage:	Powder: -20°C 3 years ; 4°C 2 years ; 15°C 3 month In solvent: -80°C 6 months ; -2°C 1 month ; 10°C 1 week
Chemical Structure:	H-Lys-Pro-Val-OH

ANALYTICAL DATA

Test Items	Specifications	Results
Appearance:	White to off-white lyophilized solid powder	Conforms
Purity (HPLC):	>98.7%	98.9%
TFA Content:	<0.50%	Conforms

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

KPV (free base) is white to off-white lyophilized powder. Based on the publicly available literature, KPV (free base) is soluble in water up to 0.70 mg/mL.[20]

For topical drug products such as creams, solubility and particle size are generally important characteristics for BDS that need to be controlled to ensure potency uniformity. If BDS is soluble in the vehicle, then potency uniformity would be based largely upon adequate distribution of the component throughout the mix. If the BDS is insoluble in the vehicle, then in addition to assuring uniformity of distribution in the mix, potency uniformity depends upon control of particle size, and use of a validated mixing process. Particle size can also affect the activity of the drug substance because the smaller the particle size the greater its surface area, which may influence its activity.

Because the nominator did not provide any information on how to compound proposed cream or gel final product, especially what vehicle will be used, we cannot evaluate how the

[20] See the CoA for KPV 2 mg, available at: https://www.uk-peptides.com/image/catalog/COA/COA%20PEPTIDES%20WEBSITE%2042.pdf. Accessed August 26, 2024.

physicochemical characteristics of KPV (free base), especially solubility and particle size, will impact the performance of the proposed final product(s).

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 a lack of CoA for KPV (free base), we do not know if microbiological tests, which are required for topical products, are in place to control microbiological quality of the BDS proposed for compounding cream/gel dosage form. Lack of control of microbiological quality of a BDS (e.g., establishing an acceptable level of microorganisms) may affect physical/chemical stability or effectiveness of product. No such relevant information was identified in the public domain.

Conclusions: KPV (free base) is reported to be a small peptide consisting of three amino acids, including lysine (K), proline (P), and valine (V). As reported in the literature, KPV (free base) is expected to be stable for up to 3 years when stored at -20°C.

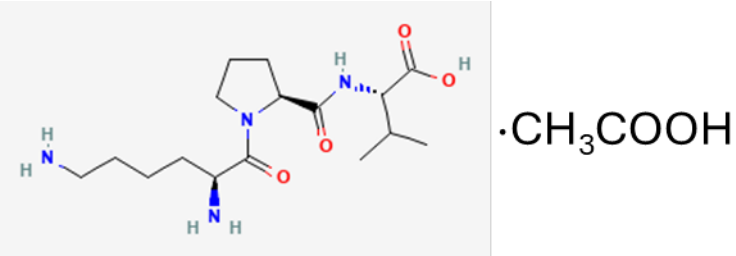
KPV (free base) is deemed to be not well-characterized from the physical and chemical characterization perspective because (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., INN, IUPAC, USAN), and (2) BDS specific quality control attributes, including impurities, aggregates, and microbiological tests, were not found in the publicly available scientific literature and lack of a CoA in the nomination package which are offered as evidence to establishing identity, purity, and impurity profiles of the substance.

In addition, due to lack of information on the formulation of proposed cream/gel final products, we cannot evaluate how the physical and chemical characteristics, especially limited water solubility (0.7 mg/mL) and particle size, impact the performance of final products.

2. KPV Acetate

KPV acetate is reported to be an acetate salt form of KPV (free base) peptide of three amino acids. The molecular formula of KPV acetate is $C_{16}H_{30}N_4O_4 \cdot CH_3COOH$ and its molecular weight is 402.5 g/mol. The chemical structure of KPV acetate is shown in Figure 3.

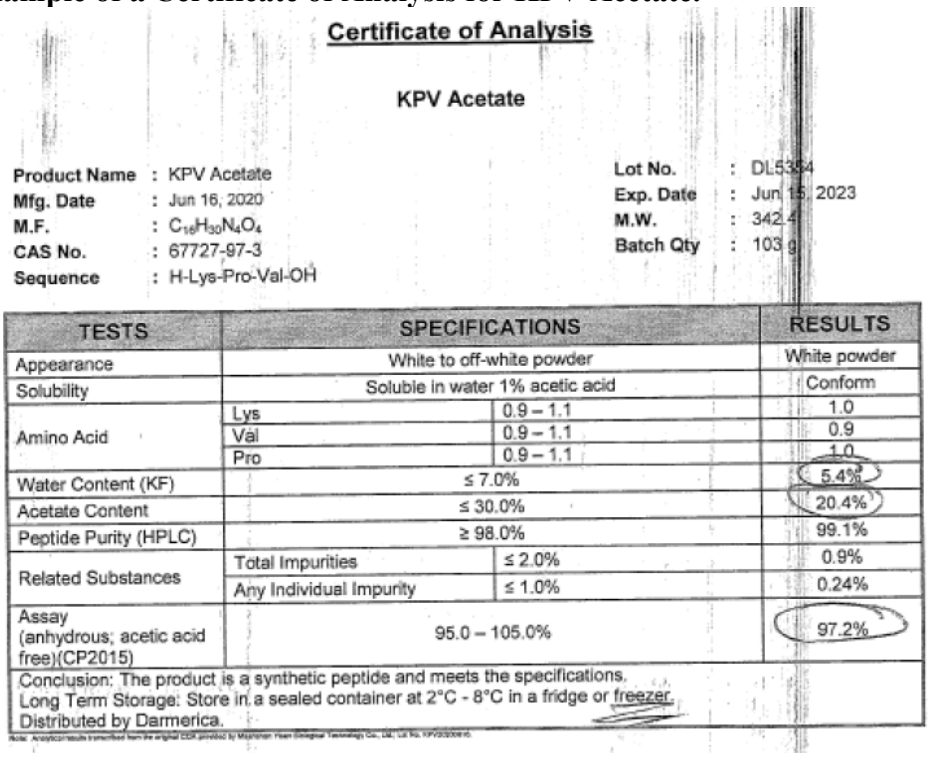
Figure 3. The Chemical Structure of KPV Acetate.



The nominator provided the following CoA for KPV acetate with the quality control attribute testing results, including identification, amino acid composition, assay, related substances

(impurities), water content and acetate content (Figure 4). There are no testing results for the quality control attribute on aggregates and microbiological testing levels.

Figure 4. Example of a Certificate of Analysis for KPV Acetate.



Certificate of Analysis

KPV Acetate

Product Name : KPV Acetate
Mfg. Date : Jun 16, 2020
M.F. : $C_{16}H_{30}N_4O_4$
CAS No. : 67727-97-3
Sequence : H-Lys-Pro-Val-OH

Lot No. : DL5354
Exp. Date : Jun 15, 2023
M.W. : 342.4
Batch Qty : 103 g

TESTS	SPECIFICATIONS		RESULTS
Appearance	White to off-white powder		White powder
Solubility	Soluble in water 1% acetic acid		Conform
Amino Acid	Lys	0.9 – 1.1	1.0
	Val	0.9 – 1.1	0.9
	Pro	0.9 – 1.1	1.0
Water Content (KF)	≤ 7.0%		5.4%
Acetate Content	≤ 30.0%		20.4%
Peptide Purity (HPLC)	≥ 98.0%		99.1%
Related Substances	Total Impurities	≤ 2.0%	0.9%
	Any Individual Impurity	≤ 1.0%	0.24%
Assay (anhydrous; acetic acid free)(CP2015)	95.0 – 105.0%		97.2%
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 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 KPV acetate are "in a sealed container at 2°C to 8°C".

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.

It was reported that KPV acetate forms Lys–Pro–DKP (DKP: lys–pro–diketopiperazine) as one of the major degradation products under various forced degradation conditions, including acid and alkaline hydrolysis, and oxidative degradation by H_2O_2. Under basic conditions, KPV acetate produced several nonpolar degradation products (DP1, DP2 and DP3: degradation

products without elucidation of the structure) in addition to Lys–Pro–DKP. When treated with 0.5% H_2O_2, the reaction was rapid, and KPV acetate degraded to Lys–Pro–DKP, proline and valine.[21]

b. Probable Routes of API Synthesis

KPV (free base) can be synthesized using the solid-phase synthesis methodology, as mentioned in A.1.b. Then, the free base can be converted into acetate form of KPV (free base).

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 KPV 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.

In the CoA the nominator provided there is total impurity limit of ≤2.0% with the testing result of 0.9% and any individual impurity limit of ≤1.0% with the testing result of 0.24% for KPV acetate. However, there is no information on the nature of single impurity in the nomination. In addition, there is no information on what synthetic method is used to produce nominated KPV acetate, it is difficult to predict the nature of individual impurity as well as peptide-related aggregates.

---

[21] See the PhD dissertation by Kasturi Pawar (Auburn University, Alabama) entitled: *Microneedle-Assisted Iontophoretic Transdermal Delivery Of Drugs*; available at: https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=394644499822140e9922599fe8efbb655f105976#:~:text=Under%20various%20forced%20degradation%20conditions%2C%20KPV%20forms,as%20shown%20in%20Fig.%205.4A%2C%205.4B%20and. Accessed April 10, 2025.

[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. When 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 D.I. as part of the safety assessment of the substance.

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

KPV acetate is a white to off-white solid powder. It is reported to dissolve in water at 5 mg/mL.[23] Therefore, water solubility and particle size will not be issues of concern for the proposed cream/gel dosage forms.

e. Any Other Information About the Substance That May Be Relevant, Such as Whether the Bulk Drug Substance is Poorly Characterized or Difficult to Characterize Polymorphism

In the CoA the nominator provided, there is no testing data for microbiological quality control of KPV acetate, which are required for topical products, to control the BDS proposed for compounding cream/gel dosage forms. Lack of control of microbiological quality of a BDS (e.g., presence of unacceptable level of microorganisms) may affect the physical/chemical stability, safety, or effectiveness of the product. No such relevant information was identified in the public domain.

Conclusions: KPV acetate is reported to be an acetate salt form of KPV (free base) peptide consisting of three amino acids. As reported in the literature, KPV acetate is expected to be stable under reported storage conditions (at 2°C to 8°C).

KPV acetate is deemed 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) lack of information on the nature of individual impurity, potential peptide related aggregates, as well as microbiological testing data, none of which were found in the CoA or reported in publicly available scientific literature.

In addition, due to lack of information on the formulation of proposed cream/gel final products, we cannot evaluate how the physical and chemical characteristics, such as particle size, impact the performance of final products.

B. Has the Substance Been Used Historically in Compounding?

This evaluation focuses on KPV (free base) and KPV acetate for the topical route of administration and its use in wound healing and inflammatory conditions; however, FDA searched generally for information on the historical use of KPV (free base) and KPV 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

[23] See the PeptideSciences website for KPV 5 mg, available at: https://www.peptidesciences.com/kpv-5mg. Accessed August 26, 2024.

(OF) Product Reporting Database.[24] It is often unclear whether the KPV discussed in this section 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.

The earliest and extent of KPV (free base) and KPV acetate use in compounding is unknown. No published studies were found in which non-compounded or compounded drug products containing KPV (free base) or KPV acetate were used in humans. According to OF reports submitted to the FDA, OFs have not reported preparing single or multiple-API compounded drug products containing KPV (free base) or KPV acetate from January 2017 to June 2025.[25]

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

Results from a Google search indicate that KPV as a single ingredient and in combination with other substances is promoted on websites.

The websites assert that single ingredient KPV is used for a wide array of inflammatory conditions, improves wound healing and skin health, strengthens the immune system, protects against nerve damage and stroke,[26] promotes gut health, acts as an antimicrobial, reduces tumor growth in the body (Appendix 1), and is effective in treating psoriasis.[27] KPV is also promoted for inflammatory bowel diseases, colitis, and Crohn's disease.[28] It is promoted as helpful in mast cell activation syndrome, histamine intolerance, recovery from COVID-19, Lyme disease, mold toxicity, and pain syndromes.[29] It is unclear whether compounded products are being used in all of these instances.

---

[24] See the FDA Outsourcing Facility Product Report Database, available at: https://www.accessdata.fda.gov/scripts/cder/outsourcingfacility/.

[25] 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. See the FDA Outsourcing Facility Product Report Database, available at: https://www.accessdata.fda.gov/scripts/cder/outsourcingfacility/.

[26] See the GeneMedics website for KPV, available at: https://www.genemedics.com/kpv. Accessed 2/10/24.

[27] See the Guyer Consulting webpage on immune peptides, available at: https://guyerwc.com/peptides/. Accessed 8/15/24.

[28] See the website of Dr. Toni Varela on peptide therapy, available at: https://www.drtonivarela.com/peptide-therapy. Accessed 2/10/24.

[29] See the Peak Health Institute website on KPV, available at https://www.peakhealthinstitute.com/the-power-of-kpv-peptide-a-game-changer-in-functional-regenerative-medicine/. Accessed 12/4/25.

KPV is promoted as a compounded drug product in combination with BPC-157, TB-500, AOD9604, and Follistatin-344 as a "regenerative combo" for muscle, joint, and cartilage repair.[30]

3. How Widespread Its Use Has Been

Results from an internet search for compounded drug products containing KPV (free base) or KPV acetate revealed that online websites offer options for obtaining KPV from compounding pharmacies through use of telemedicine and online consultations.[31] Several websites promote KPV as single-API injectable[32], oral[33], topical, and nasal spray[34] drug products, as well as multi-API products containing substances such as BPC-157, TB-500, AOD-9604, and Follistatin-344.[35]

OFs have not reported compounding drug products containing KPV (free base) or KPV acetate from 2017 to June 2025.

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

A search of the European Pharmacopoeia (11.8 edition, 2025), and the Japanese Pharmacopoeia (18th Edition) did not show any monograph listings for KPV (free base) or KPV acetate. The European Medicines Agency did not list any products containing KPV (free base) or KPV acetate that are authorized for use.

Conclusions: It is often unclear whether the KPV discussed in the sources considered for this section are the salt formulation or the free base. Available literature indicates that the extent of KPV (free base) or KPV acetate use in compounding is unknown. Published literature did not reveal studies in which compounded drug products containing KPV (free base) or KPV acetate were used in humans. According to the Outsourcing Facility Product Reports, outsourcing facilities did not report compounding drug products containing KPV (free base) or KPV acetate. Based on internet searches, it appears that compounders promote KPV as injectable, oral, topical

---

[30] See the Age Management of West Michigan website on KPV, available at: https://www.agemanagementmi.com/kpv. Accessed 8/15/24.

[31] For examples, see the following websites: The Dr. Toni Varela website on peptide therapy, available at: https://www.drtonivarela.com/peptide-therapy; the BluVida website on peptide therapy, available at: https://bluvida.com/peptide-therapy/; and the Fallon Wellness Pharmacy website, available at: https://fallonwellnesspharmacy.com/product-category/peptides/. Accessed 2/10/24.

[32] See the BluVida website on KPV peptide, available at: https://bluvida.com/encyclopedia/peptide-kpv-peptide/. Accessed 8/15/24.

[33] See the Peak Health Institute website on KPV, available at https://www.peakhealthinstitute.com/the-power-of-kpv-peptide-a-game-changer-in-functional-regenerative-medicine/; and the Age Management of West Michigan website on KPV, available at: https://www.agemanagementmi.com/kpv. Accessed 8/15/24.

[34] See the Wellness Lounge on KPV: available at https://www.akwellnesslounge.com/blog/peptide-spotlight-kpv and RegenFx Wellness, available at https://regenivwellness.com/kpv-peptide. Accessed 12/4/25.

[35] See the Wellness Lounge on KPV: available at https://www.akwellnesslounge.com/blog/peptide-spotlight-kpv and the Age Management of West Michigan website on KPV, available at: https://www.agemanagementmi.com/kpv. Accessed 12/4/25.

and nasal spray formulations. Different websites advertise that KPV (unspecified forms) may be used to suppress inflammatory conditions, to improve wound healing and skin health, and to protect against nerve damage and stroke.

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

The following databases were consulted for the preparation of this section: PubMed, Embase, ClinicalTrials.gov, DailyMed, Drugs@FDA, relevant professional healthcare organization websites, and various online clinical references and websites such as information from National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC).

The references submitted by the nominator do not clearly identify whether the KPV form was a salt formulation or the free base, and our search did not identify data, such as clinical studies, on these substances administered in humans. Therefore, throughout this section, the substances will be generally referred to as KPV unless otherwise specified as free base or acetate salt.

KPV-related BDSs were nominated for the following uses: "wound healing, inflammatory conditions (psoriasis, eczema, etc.)." The nomination cited nine literature references[36] in support of the nomination; none were studies of KPV administered in humans. The nominated uses are briefly described below.

Wound healing: A wound is a disruption of the normal structure and function of the epidermis and associated underlying tissues. Wounds are broadly classified as either acute or chronic and by their clinical presentation. Treatments vary depending on the specific wound type.[37] We note that the nominator has not provided information about what specific type of wound that KPV is intended to be used for.

Inflammatory conditions: Inflammatory conditions are diseases that affect various body organ systems. Inflammation can be either acute or chronic (Pahwa et al. 2025) and treatment may vary. The nominator listed the proposed use "Inflammatory Conditions (psoriasis, eczema, etc.)."

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 did not provide clinical evidence on the use of KPV in wound healing or inflammatory conditions. We performed our own search of published medical literature on additional relevant information on

[36] The nominator cited nine references in their nomination; eight references are studies on various alpha-MSH (alpha-melanocyte stimulating hormone is an endogenous neuropeptide a common precursor protein of all melanocortin peptides, which expresses in the pituitary gland (Singh and Mukhopadhyay 2014) derivatives conducted in animals) and one reference is on KPV delivery skin permeation using human cadaver skin.

[37] See the UptoDate website on the basic principles of wound healing, available at: https://www.uptodate.com/contents/basic-principles-of-wound-healing?search=wound%20healing&source=search_result&selectedTitle=1%7E150&usage_type=default&display_rank=1. Accessed 8/5/2024.

this substance; however, we did not identify data, such as clinical studies, on the use of KPV in humans.[38]

The nominator has not provided clinical evidence on the use of KPV in wound healing or inflammatory conditions.

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

Wounds and certain inflammatory conditions can be serious or life-threatening.

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

There are FDA-approved drug products that treat the same medical condition as those proposed for the KPV compounded drug product(s).[39] For wound healing, treatments vary depending on the specific wound type. Inflammatory conditions cover a wide variety of diseases and conditions for which treatment may vary.

Conclusions: There is a lack of evidence to evaluate the effectiveness of KPV (free base) and KPV acetate products for the nominated uses of wound healing and inflammatory conditions. The nomination did not include, and FDA did not find any information on the use of KPV (free base) or KPV acetate administered in humans. Acute and chronic wounds as well as inflammatory conditions are associated with morbidity and can be serious or life-threatening. In addition, there are currently various FDA-approved therapies with established efficacy for the management of wounds and treatment of various inflammatory diseases including psoriasis and eczema.

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

1. Nonclinical Assessment

The nominator submitted a list of 8 articles describing nonclinical studies of KPV. Five articles describe pharmacological studies of KPV (Brzoska et al. 2008; Dalmasso et al. 2008; Getting et al. 2003; Luger and Brzoska 2007; Pawar et al. 2017). Three articles describe pharmacological studies of N-acetylated KPV (Brzoska et al. 2008; Hiltz and Lipton 1989) and KPV dimer (Dalmasso et al. 2008), which are out of the scope of this evaluation and are, therefore, not discussed further.

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

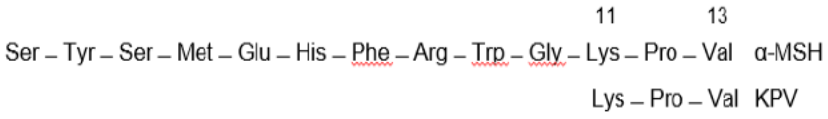
[38] See 80 FR 65765 for information necessary to fully evaluate a substance.
[39] FDA considers the existence of FDA-approved or over-the-counter (OTC) monograph drug products to treat the same condition as that proposed for the nomination relevant to FDA's consideration of the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. See 84 FR 4696.

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

a. General Pharmacology of the Drug Substance

KPV is a synthetic tripeptide (L-lysine-L-proline-L-valine) that corresponds to the amino acid sequence 11 through 13 of the endogenous melanotropic peptide αMSH (Figure 5).

Figure 5. Amino Acid Sequences of KPV and the Endogenous α-MSH.



Left to right: Amino acid sequences from N- to C-terminal domains of α-MSH and KPV. All are L-amino acids. Arg: arginine; Glu: glutamate; Gly: glycine; His: histidine; Met: methionine; Phe: phenylalanine; Pro: proline; Ser: serine; Trp: tryptophan; Tyr: tyrosine; Val: valine.

Nonclinical pharmacological studies have reported that, in vitro and in vivo, KPV has the anti-inflammatory properties but lacks the melanotropic activity of α-MSH (reviewed in Brzoska et al. 2008). Table 3, adapted from the review by Brzoska and collaborators, provides examples of in-vivo pharmacological studies reporting the anti-inflammatory effects of KPV.

Table 3. In-Vivo Anti-inflammatory Effects of KPV [Adapted From Brzoska et al. 2008].

Animal Models	Effects	ROA	Species
Skin inflammation	↓ Ear inflammation induced by topical application of picryl chloride	IP	Mouse
Skin inflammation	↓ Hind paw edema induced by local injection of ʎcarrageenan	IP	Mouse
Skin inflammation	↓ Contact dermatitis of the ear induced by topical DNFB application	IP	Mouse
Skin inflammation	↓ Hind paw edema induced by local injection of κcarrageenan	IP	Mouse
Fever	↓ Hyperthermia induced by IV injection of LP	ICV, IV	Rabbit
Fever	↓ Hyperthermia induced by IV injection of IL-1	ICV	Rabbit
GI inflammation	↓ Peritonitis with neutrophil accumulation induced by IP injection of MSU and IL-1β	SC	Mouse
GI inflammation	↓ Colitis with inflammatory cell infiltration induced by DSS	IV	Mouse
GI inflammation	↓ Colitis with inflammatory cell infiltration induced by DSS and trinitrobenzene sulfonic acid	Oral	Mouse
Brain inflammation	↓ Activation of NF-κB by ICV injection of LPS	IP	Mouse

DFNB, 2,4-Dinitrofluorobenzene; DSS, dextran sodium sulfate; GI, gastrointestinal; ICV, intracerebroventricular; IL, interleukin; IP, intraperitoneal; IV, intravenous; LP, leucocyte pyrogen; LPS, lipopolysaccharide; MSU, monosodium urate; NF-κB, nuclear factor-kappaB; ROA, route of administration; SC, subcutaneous.

The biological activities of α-MSH are mediated primarily by its ability to bind to and activate the melanocortin (MC) receptor subtypes MC1, MC3, MC4, and MC5, which are G-protein-coupled receptors. The melanotropic properties of α-MSH (i.e., the ability of α-MSH to promote the synthesis and deposit of melanin) result primarily from α-MSH-induced activation of MC1 receptor signaling in melanocytes, whereas the anti-inflammatory properties of α-MSH result primarily from α-MSH-induced activation of signaling via MC3, MC4, and MC5 receptors in different cells throughout the body (Brzoska et al. 2008). However, as discussed below, several lines of evidence suggest that MC receptors are unlikely to be the molecular targets underlying the anti-inflammatory and wound-healing properties of KPV.

In in-vitro studies, KPV was unable to displace radiolabeled α-MSH binding to rat brain tissue, murine melanoma cells, and MC1R-expressing murine macrophages (Lyson et al. 1994; Mandrika et al. 2001; Tatro and Entwistle 1994). In addition, in contrast to α-MSH, KPV did not increase cyclic AMP (adenosine monophosphate) levels in MC1 receptor-expressing murine macrophages (Mandrika et al. 2001). Finally, in-vitro and in-vivo studies using either a pharmacological or a genetic approach failed to demonstrate the involvement of MC2, MC3, and MC4 receptors in the anti-inflammatory responses and wound-healing effects induced by KPV (Getting et al. 2003).

Researchers have proposed that the following actions may contribute to the anti-inflammatory properties of KPV: (i) KPV-induced inhibition of nuclear factor-κB activation leading to a reduction in the expression of proinflammatory cytokines, and (ii) KPV-induced inhibition of the effects of proinflammatory cytokines such as interleukin 1β (Getting et al. 2003; Mandrika et al. 2001). The di/tripeptide transporter PepT1 has also been proposed to mediate the anti-inflammatory effects of KPV in the human intestinal epithelial cells Caco2-BBE and HT29-CL.19A and the human T cells Jurkat (Dalmasso et al. 2008).

Considering the anti-inflammatory properties of KPV and its effectiveness in rodent models of wound healing (Bonfiglio et al. 2006; Getting et al. 2003; Zhao et al. 2022), researchers have suggested that investigational clinical studies are needed to determine whether KPV could be used as a therapeutic intervention to promote healing of skin wounds and ulcers (Böhm and Luger 2019).

b. Pharmacokinetics/Toxicokinetics

At the time of this evaluation, the nominator did not submit, and FDA did not identify pharmacokinetic or toxicokinetic studies of KPV (free base) or KPV acetate.

According to an in-vitro study conducted in human cadaver skin, KPV does not permeate well through skin (Pawar et al. 2017). This characteristic could limit the systemic bioavailability of KPV applied topically to the skin, and, thereby, preclude systemic toxicity. However, it could also limit the potential usefulness of KPV as a topical therapeutic agent because it could prevent KPV's distribution to epidermal layers below the stratum corneum (the outermost skin layer).

Pawar and colleagues reported that strategies known to breach the structural tightness of skin, including iontophoresis and/or microneedle abrasion, increased the penetration of KPV through the stratum corneum and into the inner epidermal layers of human cadaver skin in vitro (Pawar et al. 2017). Studies are needed to determine whether strategies that facilitate the distribution of

topically applied KPV (free base) or KPV acetate through the epidermal layers of skin can also increase its systemic absorption.

c. Acute Toxicity[40]

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

d. Repeat-Dose Toxicity[41]

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

e. Genotoxicity[42]

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

f. Developmental and Reproductive Toxicity[43]

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

---

[40] 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.

[41] 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.

[42] 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.

[43] 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.

g. Carcinogenicity[44]

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

Conclusions: At the time of this evaluation, the nominator submitted, and FDA identified nonclinical pharmacological studies suggesting that KPV-related BDSs can have anti-inflammatory and wound-healing properties in in-vivo and in-vitro models. It has been suggested that the ability of KPV to inhibit the effects of inflammatory cytokines and the NF-κB-induced expression of inflammatory interleukins may contribute to the anti-inflammatory effects. However, the molecular targets underlying the pharmacological effects of KPV-related BDSs remain unknown.

Although the nominator did not submit, and FDA did not identify pharmacokinetic studies of KPV (free base) or KPV acetate, an in-vitro study reported that KPV (unidentified form) does not permeate through cadaver human skin. This low skin permeability to KPV could limit the systemic toxicity of KPV applied topically to the skin. However, it could also limit the potential effectiveness of KPV as a topical therapeutic agent because it could prevent the penetration of KPV through the stratum corneum into the lower layers of the epidermis. Strategies that can breach the tightness of the skin (e.g., iontophoresis and microneedle abrasion) have been shown to increase the skin permeability to KPV and facilitate its access to epidermal layers below the stratum corneum in vitro. It remains to be determined whether such strategies may also increase the systemic absorption of topically administered KPV (free base) or KPV acetate in vivo and, thereby, facilitate the development of untoward systemic effects. 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 KPV (free base) or KPV acetate applied topically to the skin.

2. Human Safety

The following databases were consulted in the preparation of this section: PubMed, Embase, FDA Adverse Event Reporting System (FAERS), Human Foods Program (HFP)[45] Human Foods Complaint System (HFCS)[46], 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 KPV unless otherwise specified as free base or acetate salt.

The nomination did not include, and FDA did not find information on products containing KPV (free base) or KPV acetate administered in humans.

[44] 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.

[45] Formerly the Center for Food Safety and Nutrition (CFSAN).

[46] Formerly the CFSAN Adverse Event Reporting System (CAERS).

a. Pharmacokinetic Data

FDA did not identify clinical studies in humans assessing pharmacokinetics or pharmacodynamics of KPV (free base) or KPV acetate via any route of administration.

b. Reported Adverse Reactions (Case Reports and Anecdotal Cases Assessing Safety)

FAERS

The Office of Surveillance and Epidemiology (OSE) conducted a search of the FAERS database and medical literature for reports of adverse events (AEs) associated with KPV through December 3, 2025. The FAERS search did not retrieve any reports and the literature search did not identify any cases of adverse events.[47,48]

HFCS

Human Foods Program collects reports of AEs and product complaint reports submitted to FDA for food, dietary supplements, and cosmetics in the HFCS. A search of HFCS was conducted for AEs associated with KPV for the date range of 1/1/2004 to 12/3/2025 and did not retrieve cases where KPV was administered.

We did not find case reports on the use of KPV in humans.

c. Clinical Studies Assessing Safety

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

d. Other Safety Information

Immunogenicity and Aggregation Concerns

FDA has issued guidance regarding immunogenicity assessment for therapeutic protein products.[49] The guidance describes immunogenicity as the propensity of a therapeutic protein

[47] It is important to note that FAERS data have limitations. Reporting is voluntary. In general, there is no certainty that reported adverse event was due to the suspect product. FDA does not require that a causal relationship between a product and event be proven, and the report may not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that may potentially occur with a product, especially for compounded products. Considering these limitations, FDA cannot make definitive conclusions regarding the safety of KPV based on FAERS data alone. For additional information, see Questions and Answers on the FDA FAERS website, available at: https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers. Accessed 4/23/2025.

[48] 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.

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

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 KPV (free base) and KPV acetate), which can similarly elicit an immunogenic response.

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 APIs, 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 or human exposure data assessing immunogenicity or aggregation of KPV-related BDSs. Based on available information there is insufficient data to conclude that KPV (free base) or KPV acetate do not present these risks.

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

There are FDA-approved drug products that treat the same medical conditions as those proposed for KPV-related BDSs.[50]

Conclusions: There is lack of clinical and nonclinical safety information on the use of KPV (free base) and KPV acetate. FDA is particularly concerned about the lack of any human data on drug products containing these substances administered via any route of administration, including lack of information to assess immunogenicity or aggregation of KPV-related bulk drug substances. Therefore, potential safety risks associated with the use in humans are unknown. There are currently available FDA-approved therapies for the management of wounds and to treat various inflammatory diseases.

[50] 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.

III. CONCLUSION AND RECOMMENDATION

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

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

   1.1.

   KPV (free base) is reported to be a small peptide consisting of 3 amino acids, including lysine (K), proline (P), and valine (V). As reported in the literature, KPV (free base) is expected to be stable for up to 3 years when stored at -20°C.

   KPV (free base) is deemed 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 microbiological tests, 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.

   In addition, due to lack of information on the formulation of proposed cream/gel final products, we cannot evaluate how the physical and chemical characteristics, especially limited water solubility (0.7 mg/mL) and particle size, impact the performance of final products.

   1.2.

   KPV acetate is reported to be an acetate salt of KPV peptide consisting of 3 amino acids. As reported in the literature, KPV acetate is expected to be stable under reported storage conditions (at 2°C to 8°C).

   KPV acetate is deemed 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 microbiological tests, 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.

   In addition, due to lack of information on the formulation of proposed cream/gel final products, we cannot evaluate how the physical and chemical characteristics, such as particle size, impact the performance of final products.

2. Available literature indicates that the extent of KPV (free base) or KPV acetate use in compounding is unknown. Published literature did not reveal studies in which compounded drug products containing KPV (free base) or KPV acetate were used in humans. OFs have not reported preparing single or multiple-API products containing KPV (free base) or KPV acetate. Internet search results indicate that websites promote KPV as single-API or multiple-API compounded drug products in oral, injectable, topical, and nasal spray formulations. KPV is promoted to treat inflammatory conditions, improve wound healing and skin health, and protect against nerve damage and stroke.

3. There is a lack of evidence to evaluate the effectiveness of KPV (free base) and KPV acetate products for the nominated uses of wound healing and inflammatory conditions. The nomination did not include, and FDA did not find any information on the use of these substances administered in humans. Acute and chronic wounds as well as inflammatory conditions are associated with morbidity and can be serious or life-threatening. In addition, there are currently various FDA-approved therapies with established efficacy for the management of wounds and treatment of various inflammatory diseases including psoriasis and eczema.

4. There is a lack of clinical and nonclinical safety information on the use of KPV (free base) and KPV acetate. FDA is particularly concerned about the lack of any human data on drug products containing these substances administered via any route of administration, including lack of information to assess immunogenicity or aggregation of KPV-related substances. Therefore, potential safety risks associated with the use in humans are unknown. There are currently available FDA-approved therapies for the management of wounds and to treat various inflammatory diseases.

On balance, the physicochemical characterization, information on historical use, lack of any effectiveness and safety information in humans for both KPV (free base) and KPV acetate weigh against their being added to the 503A Bulks List. In particular, FDA's proposal is based on the fact that these substances are not well-characterized from a physical and chemical characterization perspective, the extent of use in compounding is unknown, and there is non-existing information on the use of these substances administered in humans to make a conclusion on their clinical safety and effectiveness. There are currently FDA-approved therapies for the management of wounds and for the treatment of various inflammatory diseases. Accordingly, we propose not adding KPV (free base) or KPV acetate to the 503A Bulks List.

IV. REFERENCES

Böhm, M and T Luger, 2019, Are Melanocortin Peptides Future Therapeutics for Cutaneous Wound Healing? Exp Dermatol, 28(3):219-224.

Bonfiglio, V, G Camillieri, T Avitabile, GM Leggio and F Drago, 2006, Effects of the COOH-Terminal Tripeptide Alpha-MSH(11-13) on Corneal Epithelial Wound Healing: Role of Nitric Oxide, Exp Eye Res, 83(6):1366-1372.

Brzoska, T, TA Luger, C Maaser, C Abels and M Böhm, 2008, A Melanocyte-Stimulating Hormone and Related Tripeptides: Biochemistry, Antiinflammatory and Protective Effects in Vitro and in Vivo, and Future Perspectives for the Treatment of Immune-Mediated Inflammatory Diseases, Endocr Rev, 29(5):581-602.

Dalmasso, G, L Charrier-Hisamuddin, HT Nguyen, Y Yan, S Sitaraman and D Merlin, 2008, Pept1-Mediated Tripeptide KPV Uptake Reduces Intestinal Inflammation, Gastroenterology, 134(1):166-178.

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.

Getting, SJ, HB Schiöth and M Perretti, 2003, Dissection of the Anti-Inflammatory Effect of the Core and C-Terminal (KPV) α-Melanocyte-Stimulating Hormone Peptides, J Pharmacol Exp Ther, 306(2):631-637.

Hiltz, ME and JM Lipton, 1989, Antiinflammatory Activity of a COOH-Terminal Fragment of the Neuropeptide Alpha-MSH, Faseb J, 3(11):2282-2284.

Luger, TA and T Brzoska, 2007, Alpha-MSH Related Peptides: A New Class of Anti-Inflammatory and Immunomodulating Drugs, Ann Rheum Dis, 66 Suppl 3(Suppl 3):iii52-55.

Lyson, K, G Ceriani, A Takashima, A Catania and JM Lipton, 1994, Binding of Anti-Inflammatory Alpha-Melanocyte-Stimulating-Hormone Peptides and Proinflammatory Cytokines to Receptors on Melanoma Cells, Neuroimmunomodulation, 1(2):121-126.

Mandrika, I, R Muceniece and JE Wikberg, 2001, Effects of Melanocortin Peptides on Lipopolysaccharide/Interferon-Gamma-Induced NF-Kappab DNA Binding and Nitric Oxide Production in Macrophage-Like Raw 264.7 Cells: Evidence for Dual Mechanisms of Action, Biochem Pharmacol, 61(5):613-621.

Pahwa, R, A Goyal and I Jialal, 2025, Chronic Inflammation, Statpearls.

Pawar, K, CS Kolli, VK Rangari and RJ Babu, 2017, Transdermal Iontophoretic Delivery of Lysine-Proline-Valine (KPV) Peptide across Microporated Human Skin, J Pharm Sci, 106(7):1814-1820.

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

Singh, M and K Mukhopadhyay, 2014, Alpha-Melanocyte Stimulating Hormone: An Emerging Anti-Inflammatory Antimicrobial Peptide, Biomed Res Int, 2014:874610.

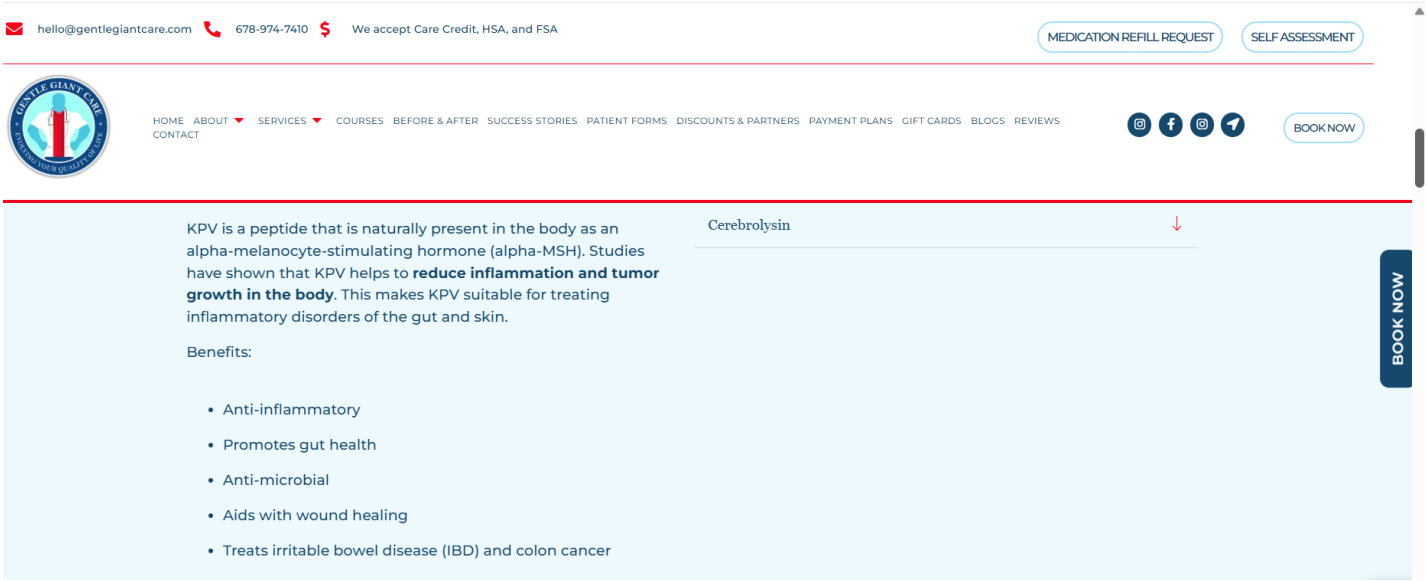
Tatro, JB and ML Entwistle, 1994, Heterogeneity of Brain Melanocortin Receptors Suggested by Differential Ligand Binding in Situ, Brain Res, 635(1-2):148-158.

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).

Zhao, Y, L Huang, G Lin, M Tong, Y Xie, H Pan, J Shangguan, Q Yao, S Xu and H Xu, 2022, Skin-Adaptive Film Dressing with Smart-Release of Growth Factors Accelerated Diabetic Wound Healing, Int J Biol Macromol, 222(Pt B):2729-2743.

V. APPENDIX

APPENDIX 1: GENTLE GIANT CARE LLC, KPV (ACCESSED 2/10/24)



KPV–Related Bulk Drug Substances (KPV (Free Base) and KPV 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?	**KPV** (lysine-proline-valine)
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?	**IUPAC Name:** (2S)-2-[[(2S)-1-[(2S)-2,6-diaminohexanoyl]pyrrolidine-2-carbonyl]amino]-3-methylbutanoic acid **Synonyms:** • Lys-pro-val • Msh (11-13) • L-Lysyl-L-prolyl-L-valine • L-Valine, N-(1-L-lysyl-L-prolyl)- • alpha-Msh (11-13) • a-MSH (11-13) (free acid) • Lysyl-prolyl-valine • ACTH-(11-13) • CTK2F5332 • DTXSID80987067

	• CHEBI:160254 • ZINC2012357 • (2S)-2-[[(2S)-1-[(2S)-2,6-diaminohexanoyl]pyrrolidine-2-carbonyl]amino]-3-methylbutanoic acid • N-[Hydroxy(1-lysylpyrrolidin-2-yl)methylidene]valine **Molecular Formula:** $C_{16}H_{30}N_4O_4$ **Amino Acid Sequence:** Lys-Pro-Val **CAS:** 67727-97-3
What is the common name of the substance?	KPV
Does the substance have a UNII code?	NO
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?	Cream/Gel
What strength(s) will be compounded from the nominated substance?	0.1%
What is the anticipated route(s) of administration of the compounded drug product(s)?	Topical
Are there safety and efficacy data on compounded drugs using the nominated substance?	Hiltz ME, Lipton JM. Antiinflammatory activity of a COOH-terminal fragment of the neuropeptide alpha-MSH. FASEB J. 1989 Sep;3(11):2282-4. PMID: 2550304. Brzoska T, Luger TA, Maaser C, Abels C, Böhm M. Alpha-melanocyte-stimulating hormone and related tripeptides: biochemistry, antiinflammatory and protective effects in vitro and in vivo, and

	future perspectives for the treatment of immune-mediated inflammatory diseases. Endocr Rev. 2008 Aug;29(5):581-602. doi: 10.1210/er.2007-0027. Epub 2008 Jul 8. PMID: 18612139. Luger TA, Brzoska T. alpha-MSH related peptides: a new class of anti-inflammatory and immunomodulating drugs. Ann Rheum Dis. 2007 Nov;66 Suppl 3(Suppl 3):iii52-5. doi: 10.1136/ard.2007.079780. PMID: 17934097; PMCID: PMC2095288. de Souza KS, Cantaruti TA, Azevedo GM Jr, Galdino DA, Rodrigues CM, Costa RA, Vaz NM, Carvalho CR. Improved cutaneous wound healing after intraperitoneal injection of alpha-melanocyte-stimulating hormone. Exp Dermatol. 2015 Mar;24(3):198-203. doi: 10.1111/exd.12609. Epub 2015 Jan 12. PMID: 25431356. Brzoska T, Böhm M, Lügering A, Loser K, Luger TA. Terminal signal: anti-inflammatory effects of α-melanocyte-stimulating hormone related peptides beyond the pharmacophore. Adv Exp Med Biol. 2010;681:107-16. doi: 10.1007/978-1-4419-6354-3_8. PMID: 21222263. Getting SJ, Schiöth HB, Perretti M. Dissection of the anti-inflammatory effect of the core and C-terminal (KPV) alpha-melanocyte-stimulating hormone peptides. J Pharmacol Exp Ther. 2003 Aug;306(2):631-7. doi: 10.1124/jpet.103.051623. Epub 2003 May 15. PMID: 12750433. Pawar K, Kolli CS, Rangari VK, Babu RJ. Transdermal Iontophoretic Delivery of Lysine-Proline-Valine (KPV) Peptide Across Microporated Human Skin. J Pharm Sci. 2017 Jul;106(7):1814-1820. doi: 10.1016/j.xphs.2017.03.017. Epub 2017 Mar 24. PMID: 28343991.
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?	Wound healing, Inflammatory conditions (psoriasis, eczema, etc)

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

KPV Acetate

Product Name : KPV Acetate
Mfg. Date : Jun 16, 2020
M.F. : $C_{16}H_{30}N_4O_4$
CAS No. : 67727-97-3
Sequence : H-Lys-Pro-Val-OH

Lot No. : DL5354
Exp. Date : Jun 15, 2023
M.W. : 342.4
Batch Qty : 103 g

TESTS	SPECIFICATIONS		RESULTS
Appearance	White to off-white powder		White powder
Solubility	Soluble in water 1% acetic acid		Conform
Amino Acid	Lys	0.9 – 1.1	1.0
	Val	0.9 – 1.1	0.9
	Pro	0.9 – 1.1	1.0
Water Content (KF)	≤ 7.0%		5.4%
Acetate Content	≤ 30.0%		20.4%
Peptide Purity (HPLC)	≥ 98.0%		99.1%
Related Substances	Total Impurities	≤ 2.0%	0.9%
	Any Individual Impurity	≤ 1.0%	0.24%
Assay (anhydrous; acetic acid free)(CP2015)	95.0 – 105.0%		97.2%
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 freezer. Distributed by Darmerica.			

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

	Name	Title	Signature	Date
Prepared by	Lionel Trilla	Assistant Manager		07/02/2020
Released by	Wilnelia Hernandez	Quality Assistant	WHR	07/06/2020

$(0.946)(0.796)(0.972) = 0.7319$

73.19%

Darmerica LLC, 198 Wilshire Blvd., Casselberry, Florida 32707, USA; Tel: (321) 219-9111; Fax: (321) 219-9130

References included with nomination FDA-2015-N-3534-0294

Capsoni F, Ongari A, Colombo G, Turcatti F, Catania A. The synthetic melanocortin (CKPV)2 exerts broad anti-inflammatory effects in human neutrophils. Peptides. 2007 Oct;28(10):2016-22. doi: 10.1016/j.peptides.2007.08.001. Epub 2007 Aug 7. PMID: 17850921.

Dalmasso G, Charrier-Hisamuddin L, Nguyen HT, Yan Y, Sitaraman S, Merlin D. PepT1-mediated tripeptide KPV uptake reduces intestinal inflammation. Gastroenterology. 2008 Jan;134(1):166-78. doi: 10.1053/j.gastro.2007.10.026. Epub 2007 Oct 17. PMID: 18061177; PMCID: PMC2431115.