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.

BPC-157 – Related Bulk Drug Substances (BPC-157 (free base) and BPC-157 acetate)

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FDA Evaluation of BPC-157 – Related Bulk Drug Substances (BPC-157 (free base) and BPC-157 acetate)

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TO: Pharmacy Compounding Advisory Committee

SUBJECT: Evaluation of BPC-157-Related Bulk Drug Substances (BPC-157 (Free Base) and BPC-157 Acetate) for Inclusion on the 503A Bulk Drug Substances List

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List of Abbreviations

Abbreviation	Term
AE	adverse event
ALT	alanine transaminase
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
AUC	area under the curve
BPC	Body Protection Compound
BDS	bulk drug substance
BET	bacterial endotoxins test
CAS	Chemical Abstracts Service
CI	confidence interval
CoA	Certificate of Analysis
CQA	critical quality attributes
DAI	Disease Activity Index
FAERS	FDA Adverse Events Reporting System
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
GI	gastrointestinal
HFCS	Human Foods Complaint System
IBD	inflammatory bowel disease
IM	intramuscular
INN	International Non-proprietary Name
IP	intraperitoneal
IUPAC	International Union of Pure and Applied Chemistry
MF/MW	Molecular Formula/ Molecular Weight
NF	National Formulary
NOAEL	no-observed-adverse-event-level
NSAID	nonsteroidal anti-inflammatory drug
ROA	route of administration
SC	subcutaneous
TG	triglyceride
UC	ulcerative colitis
USAN	United States Adopted Name

USP	United States Pharmacopeia
UNII	Unique Ingredient Identifier

I. INTRODUCTION

The Food and Drug Administration (FDA, the Agency, or we) received nominations for Body Protection Compound (BPC-157)-related bulk drug substances for inclusion on the list of bulk drug substances (BDSs) that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[1] BPC-157 is also known as Bepecin or PL-14736, which is a peptide that is reported to be comprised of 15 amino acids. Each nominator provided inconsistent information in the nomination package regarding the specific BDS proposed. Specifically, it is unclear in both packages whether the nomination was for BPC-157 acetate or BPC-157 (free base). BPC-157 acetate and BPC-157 (free base) are different active pharmaceutical ingredients and hence are considered different BDSs. Please see additional information in section II.A. The nominations were withdrawn[2] and FDA is evaluating the substances at its discretion.

Although it is unclear whether the nominators intended to nominate BPC-157 acetate or BPC-157 (free base), FDA has decided to evaluate both on its own initiative.

FDA evaluated BPC-157 (free base) and BPC-157 acetate for the treatment of ulcerative colitis (UC).[3,4]

The following BPC-157-related drug products were proposed in the nominations:

- Capsule: 250 µg, 500 µg, and 1 mg, oral
- Injection: 2,000 µg/mL, subcutaneous (SC)

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[1] There were two nominators of BPC-157-related BDSs: Wells Pharmacy Network and LDT Health Solutions. The nomination of "BPC-157" from Wells Pharmacy Network (Document ID: FDA-2015-N-3534-0279) can be accessed at: https://www.regulations.gov/document/FDA-2015-N-3534-0279. The nomination of "BPC-157" from International Peptide Society (LDT Health Solutions) (Document ID: FDA-2018-N-2973-0002) can be accessed at: https://www.regulations.gov/document/FDA-2018-N-2973-0002. These nominations were withdrawn, but because FDA is evaluating BPC-157 (free base) and BPC-157 acetate on its own initiative, FDA considered information submitted in these nominations as part of this evaluation.

[2] Document IDs: FDA-2015-N-3534-0484 and FDA-2015-N-3534-0485.

[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] BPC-157 was nominated for use in UC, Crohn's disease, Celiac disease, and tendonitis. However, FDA did not evaluate the proposed uses of Crohn's disease, Celiac disease, and tendonitis 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 using BPC-157 in these populations. See 80 FR 65765 for information necessary to fully evaluate a substance.

- Nasal spray solution: 50 µg/spray (500 µg/mL), nasal
- Suppository: 1 mg, rectal
- Transdermal cream

There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for BPC-157 (free base) or its acetate form, and neither is a component of an FDA-approved drug. BPC-157 is marketed in the United States as an ingredient in dietary supplement products formulated as oral capsules and tablets. There is no USP dietary supplement monograph for BPC-157 (free base) or its acetate form.

We have evaluated publicly available data on the 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 both BPC-157 (free base) and BPC-157 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).

II. EVALUATION CRITERIA

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

BPC-157 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. 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 bulk drug substance than the physician ordered. From a chemical analysis standpoint, inconsistent naming conventions for

[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.

BPC-157-related bulk drug substances also introduce risks because of the inability to determine which bulk drug substance 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 moiety.[10] 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 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.

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

[9] 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."

[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.

Table 1. Summary of Basic Information on BPC-157 (Free Base) and BPC-157 Acetate.

Characteristic	BPC-157 (free base)	BPC-157 Acetate
UNII Code	8ED8NXK95P	PAR2FC72XP
CAS No*	137525-51-0	216441-37-1
MF/MW (g/mol)	$C_{62}H_{98}N_{16}O_{22}$/1419.5	$C_{62}H_{98}N_{16}O_{22}$. X($C_2H_4O_2$)/NA
Chemical Structure	H-Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val-OH	H-Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val-OH.XCH_3CO_2H
Supplier[11]	Yes	Yes
Active Moiety	BPC-157 (free base)	BPC-157 (free base)

*CAS = Chemical Abstracts Service

Two nominations were submitted, which, as discussed above, were later withdrawn. Due to inconsistencies in the nomination packages, the nominated BDS is unclear from both nominators of BPC-157-related BDSs. For example, the nominated BDS is not consistent with what is listed in the Certificate of Analysis (CoA). All chemistry related information about the BDSs provided by both nominators is summarized in Table 2.

Table 2. Summary of Information Submitted in Two Withdrawn Nominations.

Nominator	1	2
Nominated BDS	BPC-157	BPC-157
BDS per UNII code	8ED8NXK95P *(matches BPC-157 free base)*	8ED8NXK95P *(matches BPC-157 free base)*
CoA	CoA provided for BPC-157 Acetate	CoA provided for BPC-157 Acetate
CAS No.	137525-51-0 *(matches BPC-157 free base)*	137525-51-0 *(matches BPC-157 free base)*
MF	$C_{62}H_{98}N_{16}O_{22}$ *(provided in the CoA, matches BPC-157 free base)*	$C_{62}H_{98}N_{16}O_{22}$ *(provided in the CoA, matches BPC-157 free base)*
MW	1,419.54 *(provided in the CoA, matches BPC-157 free base)*	1,419.54 *(provided in the CoA, matches BPC-157 free base)*

[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.

Chemical Name	H-Gly-Glu-Pro-Pro-Pro-Gly- Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val-OH *(provided in the CoA,* *matches BPC-157 free base)*	Gly-Glu-Pro-Pro-Pro-Gly- Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val *(provided in the CoA,* *matches BPC-157 free base)*
Proposed Products	Oral capsules 250 µg, 500 µg, 1 mg SC Injection 2,000 µg/mL Nasal Spray Solution 50 µg/spray (500 µg/mL) Rectal Suppository 1 mg/each	Oral capsules 500 mcg/capsule SC Injectable 2,000 mcg/mL Transdermal Cream

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

FDA is choosing to concurrently evaluate both BDSs (BPC-157 (free base) and BPC-157 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 nominators proposed to compound this BDS into the following dosage forms:

- Injection/SC injection

  For an injection product, in general, critical quality attributes (CQAs) include sterility, bacterial endotoxins test (BET), and foreign particulates are considered safety factors. For this reason, bioburden load (i.e., microbial enumeration test) and BET are critical quality considerations given the proposed use of the BDS in compounded injectable products. Evaluation of the solubility of the BDS is considered to ensure that no precipitates are formed in the compounded drug product.

- Oral capsule

  For an oral dosage form such as capsule, in general, CQAs include dissolution and microbial quality. For this reason, microbial test and particle size distribution are critical quality considerations given the proposed use of the BDS in compounded oral capsules.

- Transdermal cream

  For transdermal cream product, in general, CQAs include rheological properties, emulsion globule size, particle size (for suspended solid BDS) or crystal formation (for dissolved BDS), content uniformity, and microbial quality of the BDS. For this reason, particle size (for suspended solid BDS) and microbial limit are critical quality considerations given the proposed use of the BDS in compounded transdermal cream.

- Nasal spray solution

  The container closure system including container, closure, and pump are considered critical components of metered-dose nasal spray solution products. The CQAs for nasal spray device include pump delivery, spray content uniformity, spray pattern and plume

geometry, and droplet size distribution. However, there is a lack of information about what type of device (e.g., metered-dose nasal spray container closure system) would be used to deliver BPC-157, nor any information for a control strategy to assure the product CQAs which are critical for the safety and effectiveness of the compounded product. Other CQAs for solution-based nasal spray products include microbial quality, foreign particulates, and leachables. As such, the microbial quality of the BDSs to be used in compounding the nasal spray solution formulation, and suitability/compatibility of the device components with the formulation are critical quality considerations. Evaluation of the solubility of the BDS is also considered to ensure complete dissolution upon formulation.

- Rectal suppository

  For rectal suppository product, in general, CQAs include drug release rate (for suspended solid BDS), content uniformity, softening time of lipophilic suppositories, and microbial quality. For this reason, particle size (for suspended solid BDS) and microbial limit are critical quality considerations given the proposed use of the BDS in compounded rectal suppository.

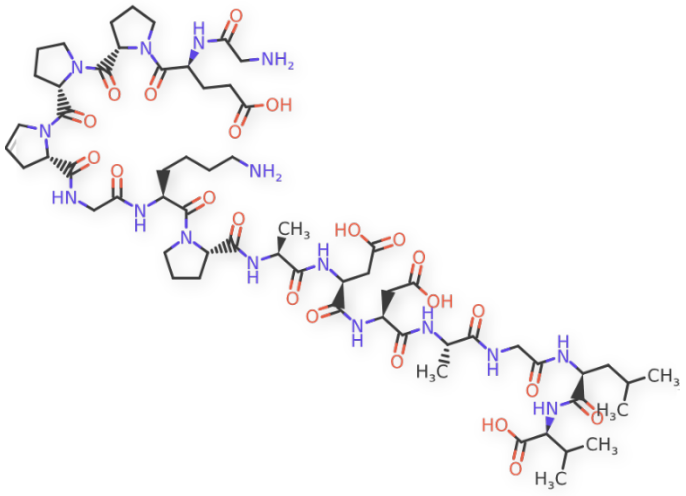
There is no USP drug substance monograph for BPC-157 free base or its acetate salt form. We reviewed physical and chemical characterization-related information provided by the nominators and performed a literature search. Databases searched for information on BPC-157 (free base) and its acetate form in preparation of this section include SciFinder, Analytical Profiles of Drug Substances, PubMed, the European Pharmacopoeia, and the USP-NF.

1. BPC-157 (Free Base)

BPC-157 (free base) is reported to be a pentadecapeptide fragment of BPC (H-Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val-OH) that has been found in gastric juice as shown in Figure 1. The melting point of BPC-157 is >232°C.[12] The molecular formula of BPC-157 (free base) is $C_{62}H_{98}N_{16}O_{22}$, and its molecular weight is 1419.5 g/mol. CoAs for BPC-157 (free base) were not included in either nomination package.

[12] https://www.chemicalbook.com/ProductChemicalPropertiesCB81343566_EN.htm. Accessed June 26, 2024.

Figure 1. The Structure of BPC-157 (Free Base). [13]



a. Stability of the API and Likely Dosage Forms

It is reported that lyophilized BPC-157 (free base) is stable at room temperature for 3 weeks. However, it is recommended to be stored desiccated below -18°C because exposure to moisture will greatly decrease long-term stability of lyophilized peptides.[14] Upon reconstitution, BPC-157 (free base) in solution is stable for 2-3 weeks stored at 4°C and for 3-4 months at -20°C.[15]

FDA notes that peptides such as BPC-157 (free base) 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, such as BPC-157 (free base), 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. 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. Significant amounts of aggregates can form in formulated products, especially during storage or when exposed to stress conditions.

b. Probable Routes of API Synthesis

BPC-157 (free base) was first synthesized by researchers at University of Zegreb, Republic of Croatia, in the early 1990s. In 1993, BPC-157 (free base) was described to be synthesized by stepwise condensation of fluorenylmethoxycarbonyl (Fmoc) protected amino acids bonded to a polymeric carrier (benzhydrilaminoresin) using diisopropylcarbodiimide as the coupling reagent

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[13] https://gsrs.ncats.nih.gov/ginas/app/ui/substances/4e592d61-f6dd-428c-96e9-5e56148614e4. Accessed June 26, 2024.
[14] https://www.prospecbio.com/bpc-157. Accessed June 26, 2024.
[15] https://particlepeptides.com/en/buy-peptides/1-bpc-157-5mg.html. Accessed June 26, 2024.

(Sikirić et al. 1993). In each step, the Fmoc protective group was removed with piperidine, then all further amino acids were introduced using the same method until synthesis was completed. The cleavage of the peptide was done using a mixture of trifluoroacetic acid/trifluoromethanesulphonic acid/anisole (2:17:52). The raw peptide mixture was purified by high-performance liquid chromatography to a purity of >95%.

c. Likely Impurities[16]

Generally speaking, peptide-related impurities and peptide synthesis process-related impurities contribute to and are considered in the evaluation of the impurity profile for all peptides, including BPC-157 (free base). For most synthetic peptides, solid-phase synthesis methods are 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, free amino acids) and other species that may carry over into the drug substance. In addition, residual solvents, coupling reagents, activators, catalysts, and scavengers may exist as solid phase peptide synthesis process related impurities. The drug substance and its proposed product-related impurities may also include peptide-related aggregates.

There is no CoA for BPC-157 (free base) in either of the nomination packages. We conducted literature searches and found that most CoAs for BPC-157 (free base) only contain purity testing results, an example of which is shown below (Figure 2).[17] There is no information about the impurity limits/testing results in the CoA to demonstrate control of the impurity profile of BPC-157 (free base).

Because there is lack of information regarding potential impurities that can be present in BPC-157 (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.

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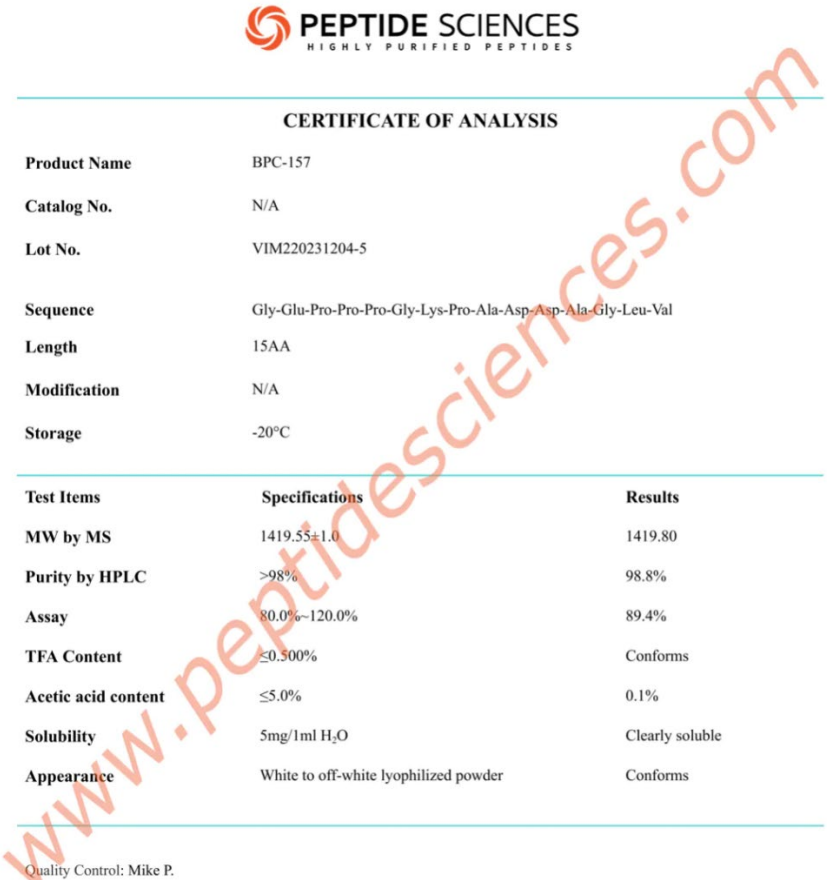
[16] This evaluation contains a non-exhaustive list of potential impurities in the bulk drug substance and does not address fully the potential safety concerns associated with those impurities. The compounder should use the information about the impurities identified in the certificate of analysis accompanying 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 II.D.1. as part of the safety assessment of the substance.

[17] https://www.peptidesciences.com/bpc-157?size=5mg. Accessed June 26, 2024.

Figure 2. Example of a CoA for BPC-157.



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CERTIFICATE OF ANALYSIS

Product Name	BPC-157
Catalog No.	N/A
Lot No.	VIM220231204-5
Sequence	Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val
Length	15AA
Modification	N/A
Storage	-20°C

Test Items	Specifications	Results
MW by MS	1419.55±1.0	1419.80
Purity by HPLC	>98%	98.8%
Assay	80.0%~120.0%	89.4%
TFA Content	≤0.500%	Conforms
Acetic acid content	≤5.0%	0.1%
Solubility	5mg/1ml H_2O	Clearly soluble
Appearance	White to off-white lyophilized powder	Conforms

Quality Control: Mike P.

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

BPC-157 (free base) is white to off-white lyophilized powder. Information on particle size was not provided in the nomination packages which maybe pertinent for process/product performance of the proposed capsule (25 µg, 500 µg, and 1 mg), suppository (1 mg/each), and transdermal cream. BPC-157 (free base) is soluble in water at 5 mg/mL.[18] Because the BDS is soluble in water and would be solubilized prior to administration, particle size is not considered a CQA that affect performance for the proposed injection dosage form (2 mg/mL) and the proposed nasal spray solution (0.5 mg/mL).

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

Because no CoA was provided in the nomination for BPC-157 (free base), it is unclear whether a bioburden load (microbial enumeration test) and/or BET is in place to control the microbiological quality of the BDS, proposed for compounding an injectable dosage form.

[18] https://www.peptidesciences.com/bpc-157?size=5mg. Accessed June 26, 2024.

Endotoxin test is considered a critical quality attribute to control microbiological quality of a BDS intended for an injection product. In addition, there is no information about residual solvent testing. No such relevant information about BPC-157 (free base) was identified from the public domain.

As mentioned at the beginning of Section II.A, for a metered-dose nasal spray solution product, the information about the container closure system (including container, closure, pump) is relevant to the CQAs (pump delivery, spray content uniformity, spray pattern and plume geometry, and droplet size distribution) for the proposed product and would affect how the BDS is delivered. However, no such information is available either in the nominations or the publicly available scientific literature.

Conclusions: BPC-157 (free base) is reported to be a pentadecapeptide fragment of BPC. As reported in the literature, BPC-157 is expected to be stable under storage conditions below -18°C.

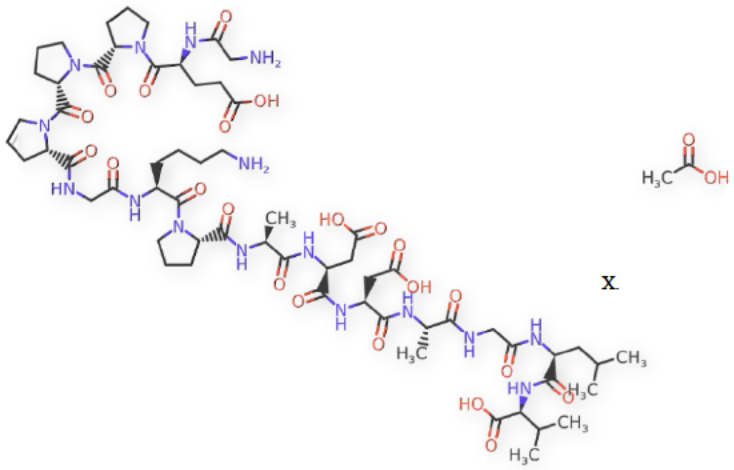
BPC-157 (free base) is considered not well-characterized from the physical and chemical characterization perspective based on (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., USAN, INN, IUPAC), and (2) data/information relevant to certain CQAs for establishing its identity, purity, and quality for its intended use in the proposed dosage forms were either lacking or deemed to be inadequate in the nomination packages or not found in the publicly available scientific literature. For example, some of this data/information include but are not limited to testing for CQAs relevant to characterizing peptide-related impurities and aggregates, microbial quality (bioburden, bacterial endotoxins), particle size, or other CQAs as dictated by dosage form (e.g., injection, metered-dose spray solution, capsule, topical cream, suppository) and route of administration (ROA) (SC injection, transdermal, nasal, oral, rectal). Additionally, FDA would have strong concerns about the use of this BDS in the proposed compounded nasal spray solution product due to lack of information about the container closure system (including container, closure, pump) – all of which are relevant to the CQAs for the proposed product and would affect how the BDS is delivered via this product.

Further, FDA is concerned about the potential for immunogenicity of BPC-157 (free base) when formulated in an injectable dosage form due to the potential for aggregation as well as potential peptide-related impurities, as discussed in the *Likely Impurities* section II.A.1.c. We also note that the stability, pharmacological activity, and immunogenic properties of peptides are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

2. BPC-157 Acetate

BPC-157 acetate is reported to be a salt of BPC-157 (free base) peptide of fifteen amino acids. The molecular formula of BPC-157 acetate is $C_{62}H_{98}N_{16}O_{22}.\ X(C_2H_4O_2)$, and its structure is shown in Figure 3. Both nomination packages included COAs for BPC-157 acetate with the testing attribute results, including appearance, identification, purity, solubility, related substances (unspecified impurity), and acetic acid content. There were no testing results for the quality control attributes on specified impurities, aggregates, bioburden load (microbial enumeration test) and/or bacterial endotoxin levels.

Figure 3. The Structure of BPC-157 Acetate.[19]



a. Stability of the API and Likely Dosage Forms

Based on the CoAs provided by the nominators, long-term storage conditions for BPC-157 acetate are "in a sealed container at 2°C to 8°C in a fridge or freezer" or "-20°C under dry conditions". Additionally, BPC-157 acetate is reported to remain stable up to 4 years when stored at -20°C.[20]

FDA notes that peptides such as BPC-157 acetate 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. Multiple analytical methods may be needed to detect various aggregates, including size exclusion chromatography or field flow fractionation. Hence, peptides, such as BPC-157 acetate, may require more and/or specific analytical in-process and final 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. Significant amounts of aggregates can form in formulated products, especially during storage or when exposed to stress conditions.

[19] https://gsrs.ncats.nih.gov/ginas/app/ui/substances/855cd030-58cd-4f4d-80f0-0faa1b427d3c. Accessed June 26, 2024.
[20] https://www.caymanchem.com/product/30989/bpc-157-(acetate). Accessed June 26, 2024.

b. Probable Routes of API Synthesis

BPC-157 (free base) was synthesized as mentioned in II.A.1.b. Then, BPC-157 (free base) can be converted into BPC-157 acetate.

c. Likely Impurities[21]

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 BPC-157 acetate. For most synthetic peptides, solid-phase synthesis methods are 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, free amino acids) and other species that may carry over into the drug substance. In addition, residual solvents, coupling reagents, activators, catalysts, and scavengers may exist as solid-phase peptide synthesis process related impurities. The drug substance and its proposed product-related impurities may also include peptide-related aggregates.

In the CoA provided by nominator 1, a purity test limit of ≥95% with the testing result of 97.8%, is listed for BPC-157 acetate, and Related Substance test limit for maximum individual impurity and total impurities of ≤3.0% and ≤5.0%, respectively, with the testing results of 1.1% and 2.2%, respectively. However, the impurity profiles are unclear because the impurities were not identified or specified.

In the CoA provided by nominator 2, there is only a purity test with the testing result of 98.34%. There is no impurity attribute control to demonstrate the impurity profiles.

Therefore, we conducted literature searches and found that most of CoAs for BPC-157 acetate only contain purity testing as shown in Figure 4, the CoA from Biotech Peptides.[22]

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[21] 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 II.D.1. as part of the safety assessment of the substance.

[22] https://biotechpeptides.com/product/bpc-157/. Accessed June 26, 2024.

Figure 4. Example of a CoA for BPC-157 Acetate.

CERTIFICATE OF ANALYSIS

Lot No.	1332522
Product Name	BPC-157 Acetate
Catalog No.	N/A
Sequence	Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val
Length	15AA
Modification	N/A
Storage	-20°C

Test Items	**Specifications**	**Results**
MW by MS	1419.6±1.0	1419.1
Purity by HPLC	>98%	98.2%
Assay	80.0%~120.0%	100.8%
TFA Content	N/A	N/A
Acetic acid content	N/A	N/A
Moisture content	N/A	N/A
Solubility	5mg/1ml H_2O	Clearly soluble
Appearance	White to off-white lyophilized powder	Conforms

Report Date：22 Dec 2023

Because there is a lack of information regarding potential impurities that can be present in BPC-157 acetate and the potential of peptide aggregation, we cannot rule out the potential for immunogenicity associated with these impurities and peptide-related aggregates.

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

BPC-157 acetate is a white to off-white solid powder. Information on particle size was not provided in the nomination packages but may be pertinent for process/product performance of the proposed capsule (25 µg, 500 µg, and 1 mg), suppository (1 mg/each), and transdermal cream. It is soluble in water at 5 mg/mL.[23] Because the BDS is soluble in water and would be solubilized prior to administration, particle size is not considered a CQA that affect performance

[23] https://biotechpeptides.com/product/bpc-157/. Accessed June 26, 2024.

for the proposed injection dosage form (2 mg/mL) and the proposed nasal spray solution (0.5 mg/mL).

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

No bioburden/endotoxin test is mentioned in the CoA provided by the nominator. Endotoxin test is considered a critical quality attribute to control microbiological quality of a BDS intended for an injection product. In addition, there is no information about residual solvent testing. No such relevant information for BPC-157 acetate was identified in the public domain.

As mentioned at the beginning of Section II.A, for a metered-dose nasal spray solution product, the information about the container closure system (including container, closure, pump) is relevant to the CQAs (pump delivery, spray content uniformity, spray pattern and plume geometry, and droplet size distribution) for the proposed product and would affect how the BDS is delivered. However, no such information is available either in the nominations or the publicly available scientific literature.

Conclusions: BPC-157 acetate is reported to be a salt of BPC-157 (free base) peptide of fifteen amino acids. As reported in the literature, BPC-157 acetate is expected to be stable under reported storage conditions below -20°C.

BPC-157 acetate is considered not well-characterized from the physical and chemical characterization perspective based on (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., USAN, INN, IUPAC), and (2) data/information relevant to certain CQAs for establishing its identity, purity, and quality for its intended use in the proposed dosage forms were either lacking or deemed to be inadequate in the nomination packages or not found in the publicly available scientific literature. For example, some of this data/information include but are not limited to testing for CQAs relevant to characterizing peptide-related impurities and aggregates, microbial quality (bioburden, bacterial endotoxins), particle size, or other CQAs as dictated by dosage form (e.g., injection, metered-dose spray solution, capsule, topical cream, suppository) and ROA (SC injection, transdermal, nasal, oral, rectal). Additionally, FDA would have strong concerns about the use of this BDS in the proposed compounded nasal spray solution product due to lack of information about the container closure system (including container, closure, pump) – all of which are relevant to the CQAs for the proposed product and would affect how the BDS is delivered via this product.

Further, FDA is concerned about the potential for immunogenicity of BPC-157 acetate when formulated in an injectable dosage form due to the potential for aggregation as well as potential peptide-related impurities, as discussed in the *Likely Impurities* section II.A.1.c. We also note that the stability, pharmacological activity, and immunogenic properties of peptides 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?

This evaluation focuses on BPC-157 (free base) and BPC-157 acetate for oral, SC, nasal, rectal, and transdermal administration and its use in UC; however, FDA searched generally for information on the historical use of BPC-157 (free base) and BPC-157 acetate in compounding. Information about use may not specify specific attributes of the product, such as ROA. Databases searched for information on BPC-157-related BDSs for this evaluation included PubMed,[24] Embase,[25] Natural Medicines,[26] Compounding Today,[27] The International Journal of Pharmaceutical Compounding,[28] United States Pharmacopeia-National Formulary,[29] European Pharmacopoeia,[30] Japanese Pharmacopoeia,[31] International Pharmacopeia,[32] globalEDGE,[33] Google and Outsourcing Facility Product Reporting Database.[34] It is often unclear whether the BPC-157 discussed in this section is the salt formulation or the free base and whether it was compounded or not. FDA will consider the information discussed in this section for both the free base and salt form.

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

The withdrawn nominations did not provide historical use data. Literature shows that BPC-157 was first described in 1993. In a 1993 article, the authors referred to BPC-157 as a "possible endogenous free radical scavenger and organoprotection mediator" (Sikirić et al. 1993). An article from 2021 discusses the use of a compounded formulation of BPC-157 (Lee and Padgett 2021). Although BPC-157 has been studied since at least 1993, there is insufficient information available to determine how long BPC-157-related BDSs have been used specifically in pharmacy compounding.

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

According to the published studies found in the literature, interstitial cystitis, knee pain and UC are the uses of BPC-157-related BDSs examined (Lee and Padgett 2021; Ruenzi et al. 2005; Lee et al. 2024). One of the studies mentioned that a compounded combination of thymosin-beta-4 (TB4) and BPC-157 was used in patients with knee pain (Lee and Padgett 2021). Another study mentioned that two patients received compounded BPC-157 infusions at doses of 10 mg and 20

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[24] Available at https://pubmed.ncbi.nlm.nih.gov/. Accessed December 4, 2025.
[25] Available at https://www.embase.com/search/quick?phase=continueToApp. Accessed December 4, 2025.
[26] Available at https://naturalmedicines.therapeuticresearch.com/ (subscription required). Accessed December 4, 2025.
[27] Available at https://compoundingtoday.com (subscription required). Accessed December 4, 2025.
[28] Available at https://ijpc.com/ (subscription required). Accessed December 4, 2025.
[29] Available at https://www.uspnf.com/ (subscription required). Accessed December 4, 2025.
[30] Available at https://pheur.edqm.eu/home (subscription required). Accessed December 4, 2025.
[31] Available at https://www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0029.html. Accessed December 4, 2025.
[32] Available at https://digicollections.net/phint/2025/index.html#p/home. Accessed December 4, 2025.
[33] Available at https://globaledge.msu.edu/industries/pharmaceuticals/regulatory-agencies. Accessed December 4, 2025.
[34] Available at https://www.accessdata.fda.gov/scripts/cder/outsourcingfacility/. Accessed December 4, 2025.

mg (Lee and Burgess 2025). Another study mentioned that patients received compounded "intravesical injections of 1 mg BPC-157, placed in 10 spots (total of 10 mg) in the uroepithelium of the bladder wall" (Lee et al. 2024). However, it is unclear if the product used in patients with UC was compounded (Ruenzi et al. 2005). A clinic mentioned on their website that BPC-157 "has been called 'wolverine compound' by many due to its intense healing properties."[35] An FDA Adverse Events Reporting System (FAERS) case report described the use of a compounded BPC-157 acetate 15 mg per vial injection product for inflammation and injury. Another case report described a compounded BPC-157 injection product that was provided by a compounding pharmacy for which the reason for use was not stated. A third case report described a patient who received a BPC-157 and TB-500 (5mg/5mg) injection product labeled for "research purposes only" and subsequently developed significant adverse reactions while following a joint and wound healing peptide protocol. (See Section II.D.2.b for additional details).

3. How Widespread Its Use Has Been

According to the FDA's outsourcing facility product reporting data from January 2017 to June 2025, there were no reported compounded drug products containing BPC-157 (free base) or BPC-157 acetate.[36] An article noted that "In June 2024, the 'BPC-157' Google search volume index, which measures the popularity of a search query, was at an all-time high. Concurrently, there are over 50 million 'BPC-157' tagged video views on both YouTube and TikTok, with over 100,000 members in peptide-related Reddit communities" (Vasireddi et al. 2025). A Google search for BPC-157 generally identified websites of compounding pharmacies as well as several med spas and clinics in the United States that mentioned BPC-157 for a variety of uses, including:

- "to support: muscle, joint health, digestion and the normal function of the gut-brain axis";[37]
- "decrease inflammation of the stomach and intestines, which can improve irritable bowel syndrome, stomach ulcers, chron's [*sic*] disease, and ulcerative colitis";[38]
- "prevent ulcers of the stomach";[39]
- "to support gastrointestinal system balance, cellular wellness, and internal resilience";[40]

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[35] Anderson Longevity Clinic, https://andersonlongevityclinic.com/bpc157. Accessed December 4, 2025.
[36] 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. The outsourcing facility product report is available at:https://www.accessdata.fda.gov/scripts/cder/outsourcingfacility/.
[37] Palm Harbor Pharmacy, https://palmharborpharmacy.com/product/bpc-157-rapid-250mcg-60c/. Accessed December 4, 2025.
[38] Groov Wellness, https://groovhealthwellness.com/peptide-therapy/. Accessed December 4, 2025.
[39] Stemedix, https://stemedix.com/peptides/. Accessed December 4, 2025.
[40] Compounding Pharmacy of America, https://compoundingrxusa.com/product/bpc-157-pure/. Accessed December 4, 2025 .

- "mental, gastrointestinal, cardiac, and autoimmune health";[41] and
- "accelerate the healing of injuries and wounds, including gastric ulcers, tendons, ligaments and bones."[42]

BPC-157 drug products are marketed as capsule, injection, oral spray, and nasal spray formulations. For example, one compounder markets BPC-157 on their website as a 500 µg capsule product with directions for patients to "take one capsule twice daily or as directed by your healthcare provider."[43] Another compounder markets a 500 µg oral spray.[44] A concierge service markets BPC-157 as a 10mg/5mL injection kit. This kit is designed for patients to self-administer at home with an optional telehealth consult.[45] One website markets lyophilized BPC-157 and BPC-157 acetate 6 mg and 10 mg single-API nasal spray products, BPC-157 and Thymosin Beta 4 Fragment 17-23 multiple-API nasal spray products (10 mg/25 mg and 10 mg/50 mg), BPC-157 250 µg oral capsules, lyophilized BPC-157 acetate 10 mg injection product, and lyophilized BPC-157 6 and 10 mg injection products.[46] Another website markets BPC-157 and Thymosin-beta-4 (TB 500) 10 mg multiple-API injectable product as well as a BPC-157 5 mg and 10 mg product.[47] In addition, a website mentions a BPC-157 and TB 500 multiple-API product."[48] Furthermore, a website mentions BPC-157and TB 500 multiple-API products for research purposes only and not for human or veterinary use."[49] BPC-157 is listed on the World Anti-Doping Agency's prohibited list under the non-approved substances (S0) section.[50]

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

There is no monograph for BPC-157 (free base) or BPC-157 acetate in the European Pharmacopoeia (11th Edition, 11.8), Japanese Pharmacopoeia (18th Edition) or the International Pharmacopeia (12th Edition). A search in globalEDGE did not yield BPC-157 (free base) or BPC-157 acetate as a component of an approved product in any country. In addition, there are no approved products or pending applications for medicines containing BPC-157 (free base) or BPC-157 acetate in New Zealand, but the New Zealand Medicines Classification Committee

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[41] Innovative Directions in Health, https://idinhealth.com/product/bpc-157-pure-60ct/. Accessed December 4, 2025.
[42] MedClub by Dr. Jenn Concierge Aesthetics, https://drjennpb.com/product/bpc-157-injury-repair-peptide-10mg-5ml/. Accessed December 4, 2025.
[43] See footnote 39.
[44] Fallon Wellness Pharmacy, https://fallonwellnesspharmacy.com/product/integrative-peptides-bpc-157-pure-oral-spray/. Accessed December 4, 2025.
[45] See footnote 41.
[46] Limitless Biotech, https://limitlesslifenootropics.com/search.php?search_query=bp c-157. Accessed December 4, 2025.
[47]Biotech Peptides, https://biotechpeptides.com/product/bpc-157-tb-500-10mg-blend-2/. Accessed December 4, 2025.
[48] Peptide.org, https://www.peptides.org/bpc-157-tb-500-capsules/. Accessed December 4, 2025.
[49] Pure Health Peptides, https://purehealthpeptides.com/product/bpc-157-tb. Accessed December 4, 2025.
[50] World Anti-Doping Agency (WADA), https://www.wada-ama.org/en/prohibited-list?item-id=5027. Accessed December 4, 2025.

meeting held in May 2023 proposed that BPC-157 should be classified as a prescription medicine.[51]

Conclusions: As previously mentioned, it is often unclear whether the BPC-157 discussed in the sources considered for this section is the salt formulation or the free base. Therefore, FDA considered the information discussed for both the free base and salt form. BPC-157 was first described in the literature in 1993 and was referred to as a possible endogenous free radical scavenger and organoprotection mediator. Interstitial cystitis, knee pain and UC are the uses of BPC-157-related BDSs examined in the literature. Gastrointestinal (GI) uses are the most commonly mentioned uses listed on websites. BPC-157-related BDSs are marketed as an oral capsule, oral spray, nasal spray, and injectable product. However, it is unclear whether some of these products are compounded or if pharmacies are currently compounding products containing BPC-157-related BDSs. There is no approved product containing BPC-157-related BDSs in any country at this time, nor is BPC-157 (free base) or BPC-157 acetate found in the European, Japanese, or the International Pharmacopeias. Currently available data and published literature is too limited for FDA to understand the historical use of BPC-157 (free base) and BPC-157 acetate in compounded drug products.

C. 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, ClinicalTrials.gov, professional healthcare organization websites, and various online clinical references and websites. The clinical articles submitted by the nominators and those identified by FDA do not always clearly identify BPC-157 as a free base or salt. Therefore, in this section, the substance will be generally referred to as BPC-157, unless the article under discussion clearly specifies the use of the free base or the acetate salt in a study. We evaluated BPC-157 (free base) and BPC-157 acetate for the treatment of UC and considered available data to support effectiveness.

1. Ulcerative Colitis

UC is a form of inflammatory bowel disease (IBD). IBD includes a group of chronic, relapsing, immune-mediated inflammatory conditions of the GI tract. UC and Crohn's disease are two major forms of IBD.[52] Both UC and Crohn's disease are characterized by complex pathogeneses involving host genetics, gut microbiome, gut epithelial barrier, immune system, and

[51]"There are currently no approved products or pending applications for medicines containing BPC-157 in New Zealand." MEDSAFE New Zealand Medicines and Medical Devices Safety Authority, https://www.medsafe.govt.nz/profs/class/Minutes/2021-2025/mccMin25May2023.htm. Accessed December 4, 2025.

[52] As described in Section I of this evaluation, FDA did not evaluate the proposed use of Crohn's disease because the nomination did not include sufficient information for the Agency to evaluate whether the substance is appropriate for this use in compounded drug products. In addition, FDA did not identify clinical studies using BPC-157 in subjects with Crohn's disease.

environmental factors, but may differ in their clinical manifestations, and characteristic endoscopic and histologic findings.

UC involves inflammation of the rectum and may extend in a continuous fashion to more proximal portions of the colon. Endoscopic findings may range from mild edema/erythema, to frank ulcerations, friable mucosa/bleeding, and the presence of exudates. Histology is characterized by a chronic active inflammation, presence of cryptitis or crypt abscesses, and lack of granuloma formation. The annual incidence rates in North America range from 8.8 to 23.14 cases per 100,000 person-years, and the prevalence ranges from 139.8 to 286.3 cases per 100,000 persons (Ng et al. 2017). Onset of disease most commonly occurs between the second and fourth decades of life, and the clinical course is characterized by periods of remission and exacerbations (Le Berre et al. 2023). Patients with UC most commonly present with bloody diarrhea, rectal bleeding, tenesmus, urgency, and abdominal pain. Disease of moderate to severe activity may be associated with systemic signs and symptoms, including fatigue, fever, anorexia, nausea, weight loss, and dehydration. UC can also be associated with several extraintestinal manifestations affecting a wide variety of organ systems, most commonly joints, skin, eyes, kidneys, and hepatobiliary tract. Longstanding UC is associated with a risk of dysplasia and colorectal cancer.

The diagnosis of UC is based on a combination of signs and symptoms, biochemical markers, endoscopic and histologic findings. The severity of UC is generally classified as mild-to-moderate or moderate-to-severe. Several disease activity indices for UC have been developed to quantify and standardize the evaluation of clinical disease activity.

The overall goal in the treatment and management of UC is to reduce signs and symptoms of active disease, decrease the underlying mucosal inflammation, and prevent short-term (e.g., severe bleeding, bowel perforation) and long-term complications (e.g., colon cancer). The choice of therapy is guided by the disease severity, extent of disease, and presence of other manifestations (e.g., extraintestinal complications, malabsorption). Conventional therapeutic options for treatment include medications and surgery. Medication therapy includes 5-aminosalicylate (ASA) products (e.g., mesalamine), corticosteroids, antibiotics, immunomodulators (e.g., azathioprine [AZA], 6-mercaptopurine [6-MP], methotrexate [MTX]), biologic therapies (e.g., tumor necrosis factor alpha [TNFα] blockers, anti-integrin receptor blockers, anti-interleukin [IL] 12/23 agents), and small molecule therapies including sphingosine-1-phosphate [S1P] receptor modulators, and Janus kinase [JAK] inhibitors (Singh et al. 2024). Local therapy (i.e., rectal therapies) may be used before systemic therapy (e.g., oral therapies, injection therapies) as clinically indicated. Corticosteroids are not recommended for long-term use given the toxicities associated with chronic steroid use. Surgical therapy may be required in cases of UC refractory to medical management or in cases of acute severe complications from UC (e.g., toxic megacolon, colonic perforation, severe hemorrhage) (Rubin et al. 2025).

UC is a serious chronic disease, and patients with moderate to severe disease activity may experience increased morbidity and mortality when inadequately treated. Guidelines on the management of UC have been published by the American College of Gastroenterology (Rubin et al. 2025) and American Gastroenterological Association (Feuerstein et al. 2020; Ko et al. 2019). Neither of these guidelines mention BPC-157 in their recommendations for the management of UC.

a. Considerations on Establishing Effectiveness of Therapy

Studies for products intended to treat patients with UC have traditionally used clinical remission as the primary endpoint. Currently, clinical remission as measured by the 3-component modified Mayo score is used as the primary endpoint in clinical trials used to support the indication of UC. The modified Mayo Score is a multi-component endpoint consisting of rectal bleeding, stool frequency, and endoscopy sub-scores adapted from the originally published Mayo Score.[53] Of note, for drugs intended to be administered chronically, a total controlled treatment period of at least one year in duration is recommended to adequately assess both early efficacy and durability of response over time and to adequately characterize the safety profile.[54]

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

We identified a single meeting abstract reporting on the results of a multicenter, randomized, double blind, placebo-controlled study in subjects with UC (Ruenzi et al., 2005). A total of 53 subjects with mild to moderate (definition/inclusion criteria unclear) UC (definition and inclusion criteria unknown) were randomized in a 1:1 ratio to receive BPC-157 (PL 14736) enema 80 mg or placebo once daily for two weeks. The primary endpoint was a change in the Disease Activity Index (DAI) over the treatment period, with DAI defined by the authors as "a composite score of clinical, laboratory, endoscopic, and pathohistological findings" that was not clearly defined in the abstract. Forty-six subjects completed the study. Three subjects in the BPC-157 group and two subjects in the placebo group were withdrawn due to an adverse event; per the authors, withdrawals were "mainly progression of UC". One subject from each group was lost to follow-up. According to the authors, the mean change of the DAI was -3.2 points (95% confidence interval [CI] -5.58, -0.82) in the BPC-157 group and -1.6 (95% CI -3.86, 0.67) in the placebo group with an estimated difference of 1.6 points (95% CI -4.84, 1.62) between groups.

As the study was presented as a meeting abstract, several details of the trial are lacking, including but not limited to information regarding the primary endpoint (e.g., DAI), inclusion/exclusion criteria, statistical methods, and post-treatment follow-up. The data presented for this study are therefore inadequate to support the efficacy and safety of BPC-157 given as an enema for two weeks for the treatment of UC. Of note, the nominator proposed to make a rectal suppository (not a rectal enema), which would likely only reach the rectum.[55]

We did not identify any studies that administered BPC-157 via the oral, SC, nasal, or transdermal ROA in subjects with UC. Review of the literature did not reveal any additional reports of

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[53] The modified Mayo Score is a composite endpoint consisting of rectal bleeding, stool frequency, and endoscopy sub-scores, adapted from the originally published Mayo Score. The previously used physician global assessment component is excluded to reduce subjectivity and focus the evaluation on the subject's directly reported symptoms and directly observable endoscopic findings.

[54] See FDA's draft guidance for industry Ulcerative Colitis: Developing Drugs for Treatment. Available at https://www.fda.gov/media/158016/download.

[55] Methods of rectal administration may include suppositories, liquid enemas, and foams (Loew and Siegel, 2012). The distribution of drug in rectal therapies varies by dosage form and generally can be

clinical trials, clinical evidence, or anecdotal reports of effectiveness, or lack of effectiveness, of BPC-157 for the treatment of UC. Based on the available data, there is a lack of evidence to make a conclusion on the effectiveness of BPC-157 for treating UC.

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

UC is a serious chronic disease associated with increased morbidity and mortality, including life-threatening complications such as toxic megacolon, perforation, hemorrhage, venous thromboembolism and secondary infections.

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

There are FDA-approved drug products that treat the same medical condition as that proposed for the BPC-157 compounded drug product(s).[56] Table 3 and Table 4 list currently available FDA-approved drug products indicated for UC.

Table 3. Currently Approved Medications for the Treatment of Mild to Moderate UC.

Drug class	Drug	Route of administration
5-Aminosalicylates (5-ASA)	Mesalamine	Oral (delayed release and extended release), rectal (enema and suppository)
5-ASA	Olsalazine sodium	Oral
5-ASA	Balsalazide disodium	Oral
5-ASA	Sulfasalazine	Oral

Table 4. Currently Approved Medications for the Treatment of Moderate to Severe UC.

Drug class	Drug	Route of administration
Tumor necrosis factor (TNF) blocker	Adalimumab	SC
TNF blocker	Golimumab	SC and intravenous (IV)
TNF blocker	Infliximab	SC and IV
Integrin receptor antagonist	Vedolizumab	SC and IV
Janus kinase (JAK) inhibitor	Tofacitinib citrate	Oral

characterized as follows: suppositories have dispersion limited to the rectum, foam enemas extend to the sigmoid and descending colon, and liquid enemas may reach the splenic flexure (Cohen and Dalal 2015; Loew and Siegel 2012).

[56] 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.

JAK inhibitor	Upadacitinib	Oral
Human interleukin (IL 12 and 23) antagonist	Ustekinumab	SC and IV
Interleukin-23 antagonist	Guselkumab	SC and IV
Interleukin-23 antagonist	Mirikizumab-mrkz	SC and IV
Interleukin-23 antagonist	Risankizumab-rzaa	SC and IV
Sphingosine 1-phosphate (S1P) receptor modulator	Ozanimod hydrochloride	Oral
S1P receptor modulator	Etrasimod arginine	Oral

There are multiple FDA-approved corticosteroids approved for the treatment of UC. The specific indication and treatment course varies; note that in general corticosteroids are not recommended for chronic use in UC due to toxicity. Examples include (not an exhaustive list):

- Budesonide oral and rectal
- Hydrocortisone oral and rectal
- Hydrocortisone acetate rectal
- Methylprednisolone oral
- Prednisone oral

There are several additional FDA-approved drugs that have been used off-label to treat UC such as immunosuppressants, including thiopurines (e.g., azathioprine) and calcineurin inhibitors (e.g., cyclosporine) (Rubin et al. 2025).

Conclusion: There is a lack of evidence to support the effectiveness of BPC-157 (free base) and BPC-157 acetate as a treatment for UC. There has been a single, small trial evaluating BPC-157 in the treatment of UC, however, interpretation of the results is limited by the lack of details provided in the meeting abstract and the exploratory nature of the study. We did not identify any studies that administered BPC-157 via the oral, SC, nasal, or transdermal ROA in subjects with UC. At the time of this evaluation, the data available do not support the use of BPC-157 for the treatment of UC. There are multiple FDA-approved drug products indicated to treat UC, a serious chronic disease that may cause life-threatening complications.

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

1. Nonclinical Assessment

The nominators submitted a list of 25 articles reporting the findings of nonclinical studies. Twenty four articles describe pharmacological effects of BPC-157 in different in-vivo and in-

vitro nonclinical models,[57] and one article describes the in-vitro cytoprotective effects of analogues of BPC-157 (Bodis et al. 1997).

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, National Institutes of Health's dietary supplement label database, National Toxicology Program website, Pharmapendium, PubMed, Society of Toxicology, USP, and Web of Science.

Most studies discussed in this section do not clearly identify the specific form of BPC-157 (free base or acetate) used in the different experiments. Therefore, throughout this section, we refer to BPC-157 as it is referred to in the cited studies.

a. General Pharmacology of the Drug Substance

BPC-157, the active moiety of BPC-157 (free base) and BPC-157 acetate, is a pentadecapeptide fragment of the BPC protein originally isolated from human gastric juice (Sikirić et al. 1993a). Figure 5 illustrates the amino acid sequence of BPC-157.

Figure 5. Amino Acid Sequence of BPC-157.

Left to right: Amino acid sequence from the N- to the C-terminal domain. Ala: alanine; Asp: aspartate; Gly: glycine; Glu: glutamate; Leu: leucine; Lys: lysine; Pro: proline; Val: valine. All are L-amino acids.

Since its discovery in the early 1990's, BPC-157 has been the subject of numerous publications describing its pleiotropic pharmacological effects. In short, pharmacological studies have suggested that BPC-157: (i) prevents lesions induced by different challenges in the GI and cardiovascular systems of rodents, (ii) has nephroprotective properties, (iii) promotes healing of transected tendons in rodents, and (iv) has neuroprotective properties in rodent models of stroke, encephalopathy, and spinal cord injury (Cerovecki et al. 2010; Chang et al. 2011; Gaginella 1994; Seiwerth et al. 2021; Sikiric 1999; Sikiric et al. 2011; Sikiric et al. 2012; Sikiric et al. 2016; Staresinic et al. 2003; Vukojević et al. 2022).

The paragraphs that follow focus on studies that report the pharmacological effects of BPC-157 in nonclinical models of colonic fistulas, hepatic lesions, and GI lesions as findings from these studies could be relevant to the proposed clinical application of BPC-157 in UC assessed in this evaluation.

The effects of BPC-157 on colonic fistulas have been examined in a pharmacological study conducted in adult male Wistar rats with 5-mm fistulas generated surgically at 5 cm from the anus (Klicek et al. 2008). In this study, rats were treated intraperitoneally or orally (via drinking

[57] Balenovic et al. 2009; Baric et al. 2016; Bilic et al. 2005; Blagaic et al. 2004; Chang et al. 2011; Chang et al. 2014; Crvenkovic et al. 2015; Gaginella 1994; Gjurasin et al. 2010; Gwyer et al. 2019; Huang et al. 2015; Ilic et al. 2010; Jelovac et al. 1998; Masnec et al. 2015; Mikus et al. 2001; Sebecić et al. 1999; Seiwerth et al. 1997; Sikiric et al. 1997a; Sikirić et al. 1997b; Sikiric 1999; Sikiric et al. 2016; Tohyama et al. 2004; Tudor et al. 2010; Turkovic et al. 2003.

water) with vehicle or BPC-157 (10.0 ng/kg/day or 10.0 µg/kg/day) for up to 28 days starting 30 minutes post-surgical modification. Rats were, then, euthanized on post-surgical days 1, 3, 5, 7, 14, 21, and 28, and had their colon removed at the level of the surgical fistula for a macroscopic assessment of the sizes of the fistulas. On and after post-surgical day 3, fistulas (from the skin and the colon sides) in BPC-157-treated rats were approximately 40% smaller than those in vehicle-treated rats. In addition, on post-surgical day 28, fistulas in vehicle-treated rats had reduced by <10% in size on the skin side and <25% on the colon side, whereas fistulas in BPC-157-treated rats appeared to have resolved macroscopically (Klicek et al. 2008). A dose-response relationship could not be established because the magnitude to which the two BPC-157 doses decreased the lesion sizes was comparable. The results suggest that intraperitoneal (IP) or oral treatment of rats with BPC-157 (≥10 ng/kg) improves healing of surgically generated colonic fistulas (Klicek et al. 2008). However, the data should be interpreted with caution because the authors did not provide data on the histopathological integrity of the tissue. In addition, it remains to be determined whether the BPC-157 treatment would remain effective if initiated longer after the fistulas had been generated.

Treatment of Wistar male and female rats with BPC-157 (10 ng/kg or 10 µg/kg, IP) has also been shown to prevent stomach and small intestine lesions induced by a high dose of a nonsteroidal anti-inflammatory drug (NSAID), including aspirin, indomethacin, or diclofenac (Sikiric et al. 1997a). Specifically, stomach and small intestine lesions were noted in rats: (i) 2 and 4 hours after they received a high dose of aspirin (400 mg/kg, oral gavage); and (ii) 24 hours after they received a high dose of diclofenac (125 mg/kg, IP) or indomethacin (30 mg/kg, SC). Macroscopically, the sizes of the NSAID-induced lesions were reduced by >75% in rats that were co-treated or pre-treated with BPC-157. No microscopic analysis of the tissue is included in the study, and a dose-response relationship could not be established because the two BPC-157 doses reduced the sizes of the NSAID-induced lesions to the same extent (Sikiric et al. 1997a).

The hepatoprotective effects of BPC-157 have been reported in different rat models of hepatotoxicity. For instance, hepatoprotection has been observed in adult male and female Wistar rats treated with BPC (10 ng/kg or 10 µg/kg) via oral gavage or intraperitoneally 1 hour before they were subjected to one of the following hepatotoxic challenges: (i) 24-hour bile duct and hepatic artery ligation, (ii) 48 hour-restraint stress, or (iii) tetrachloromethane treatment [1 mL/kg, IP]. BPC-157 prevented the development of liver necrosis (assessed histopathologically) and the increases in liver-associated enzymes (assessed in serum biochemistry panel) induced by each hepatotoxic challenge. A dose-response relationship was not established because the degree of hepatoprotection was comparable between the two test doses of BPC-157 (Sikiric et al. 1993b). In addition, it remains unknown whether BPC-157, used as a post-treatment after hepatotoxicity has developed, would effectively reduce the severity of the condition.

The hepatoprotective effect of BPC-157 was confirmed in a separate study in which liver damage was induced by repeated challenge of rats with the nonsteroidal anti-inflammatory drug diclofenac (12.5 mg/kg/day, IP, 3 days). In this study, BPC-157 was also shown to prevent the development of diclofenac-induced gastric lesions (Ilic et al. 2010; Ilic et al. 2011). Rats were treated with BPC-157 (10 ng/kg or 10 µg/kg) or vehicle (saline) delivered: (i) intraperitoneally immediately after each diclofenac injection or (ii) orally in drinking water during the days the rats received the diclofenac injections. The authors describe that, 3 hours after the last diclofenac injection, vehicle-treated rats presented with: (i) severe gastric, intestinal, and liver lesions; (ii)

increased serum bilirubin, aspartate transaminase (AST), and alanine transaminase (ALT); (iii) increased liver weight; (iv) brain edema; and (v) damaged neurons in different brain regions. They also report that vehicle-treated rats presented prolonged sedation/unconsciousness after the diclofenac challenges. Both the oral and the IP treatments with BPC-157 prevented the diclofenac-induced hepatic and GI lesions as well as the brain lesions and the sedation/unconsciousness (that were thought to be secondary to the hepatic damage). A dose-response relationship was not established because the protective effects of BPC-157 had the same magnitude regardless of the dose tested (Ilic et al. 2011). In addition, it remains unknown whether BPC-157 would effectively promote tissue healing if it had been used as a post-treatment after hepatic or gastric lesions induced by the different challenges were fully established.

The mechanisms of action underlying the ability of BPC-157 to prevent gastric and hepatic lesions induced by different challenges and to accelerate healing of colonic fistulas remain unknown. It is unlikely that the ability of BPC-157 to prevent the development of gastric lesions is related to modulation of gastric acid secretion or GI motility because BPC-157 has been reported to affect neither parameter (Sikiric 1999). Researchers have hypothesized that the apparent wound-healing properties of BPC-157 in different tissues could be related to its ability to up-regulate the expression of growth factors and their receptors (Chang et al. 2014; Hsieh et al. 2017), suppress release and/or expression of inflammatory factors, induce angiogenesis (Brcic et al. 2009; Huang et al. 2015; Seiwerth et al. 1997), and stimulate nitric oxide synthesis (Duzel et al. 2017; Klicek et al. 2008; Sikirić et al. 1997b).

Findings from the studies discussed above should be interpreted with caution because dose-response relationships for BPC-157 to suppress GI and hepatic injuries have not been established. In addition, the molecular targets for BPC-157 have not been identified and its mechanisms of action remain poorly understood, making it difficult to assess the biological plausibility of the pharmacological effects reported in the studies.

b. Pharmacokinetics/Toxicokinetics

A pharmacokinetic study conducted in male and female Beagle dogs and Sprague Dawley rats treated with a single IV dose of BPC-157 (free base; dogs: 6 μg/kg; rats: 20 μg/kg) revealed that the half-life ($t_{1/2}$) of BPC-157 ranges from 5.3 minutes in dogs to 15.2 minutes in rats (He et al. 2022). Since BPC-157 was reported to be resistant to hydrolysis in gastric juice in vitro (Veljaca et al. 1995), its short in-vivo $t_{1/2}$ is likely due to its hydrolysis catalyzed by blood- and/or tissue-specific peptidases.

In Sprague Dawley rats and Beagle dogs treated intramuscularly with BPC-157 (free base), the area under the curve ($AUC_{0-\infty}$) of the plots of plasma concentration vs time and the maximal plasma concentrations (C_{max}) of BPC-157 increased proportionally with increasing intramuscular (IM) doses (Table 5 and Table 6). This finding suggests that the pharmacokinetics of BPC-157 follows a first-order process.

Table 5. Pharmacokinetic Profile of BPC-157 Delivered Intramuscularly to Sprague Dawley Rats.

Dose (µg/kg)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng/mL•min)
20	12.3	75.3
100	48.9	290.0
500	141.0	1931.0

C_{max} = Maximal plasma concentration; $AUC_{0-\infty}$ = area under the curve from time 0 to infinite. Data are presented as mean or mean ± SD (n = 3 males and 3 females/dose). Table generated with data from He et al. (2022).

Table 6. Pharmacokinetic Profile of BPC-157 Delivered Intramuscularly to Beagle Dogs.

Dose (µg/kg)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng/mL•min)
6	1.05 ± 0.429	30.0 ± 3.11
30	3.30 ± 0.508	164.0 ± 21.5
150	26.10 ± 7.82	831.0 ± 246

C_{max} = Maximal plasma concentration; $AUC_{0-\infty}$ = area under the curve from time 0 to infinite. Data are presented as mean or mean ± SD (n = 3 males and 3 females/dose). Table generated with data from He et al. (2022).

Repeated treatment of rats with BPC-157 (free base; 100 µg/kg/day, IM) for 7 days resulted in an $AUC_{0-\infty}$ of 419 ng/mL•min, which is 45%). Higher than that obtained after a single IM injection of the same dose (Table 5). By contrast, repeated treatment of dogs with BPC-157 (free base; 30 µg/kg/day, IM) for 7 days resulted in an $AUC_{0-\infty}$ of 158 ± 26.0 ng/mL•min, which is comparable to that obtained after a single IM injection of the same dose (Table 6). These findings suggest that in rats, but not dogs, repeated treatment with BPC-157 may result in its accumulation.

In rats treated intravenously with the dose of 20 µg/kg and in dogs treated intravenously with the dose of 6 µg/kg, the $AUC_{0-\infty}$s of BPC-157 were 400 ng/mL•min and 76.9 ng/mL•min, respectively (He et al. 2022). Considering these findings, the IM bioavailability of BPC-157 ranges from ~18% in rats to ~39% in dogs.

After radiolabeled BPC-157 was administered intramuscularly to rats, radioactivity distributed to most tissues, peaking at 1-hour post-injection in the kidney, liver, stomach tissue, thymus, and spleen. In-vivo, BPC-157 was metabolized into shorter peptide fragments. The main routes of elimination were urine and feces (He et al. 2022).

At the time of this evaluation, the nominator did not submit, and FDA did not identify nonclinical pharmacokinetic or toxicokinetic studies of BPC-157 (free base) or BPC-157 acetate delivered via the nominated ROAs (oral, rectal, SC, transdermal, and nasal).

c. Acute Toxicity[58]

In an acute toxicity study, male and female Sprague Dawley rats and Beagle dogs treated with a single IM dose of BPC-157 (free base; 20 mg/kg and 10 mg/kg, respectively) presented with no signs of acute toxicity in addition to no histopathological alteration in various organs 14 days after the treatment. The doses of 20 mg/kg and 10 mg/kg were considered the IM no-observed-adverse-event-levels (NOAELs) in rats and dogs, respectively (Xu et al. 2020).

At the time of this evaluation, the nominator did not submit, and FDA did not identify nonclinical acute toxicity studies of BPC-157 (free base) or BPC-157 acetate, delivered via the nominated ROAs (oral, rectal, SC, and nasal). In addition, since studies were not identified to establish the absolute bioavailability of BPC-157 delivered via IM and the nominated ROAs to rats and dogs, it is not possible to use the IM NOAELs to estimate the NOAELs for the nominated ROAs. As described in the FDA's guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*,[44] NOAELs are used to predict safety margins of doses in clinical settings.

d. Repeat-Dose Toxicity[59]

Repeat-dose toxicity studies were conducted in rats and dogs treated intramuscularly for 28 days with different doses of BPC-157 (free base). Specifically, adult male and female Sprague Dawley rats and Beagle dogs were treated once daily with the BPC-157 (free base; rats: 0.2, 1.0, or 4.0 mg/kg, dogs: 0.1, 0.5, or 2.0 mg/kg). In each study, control animals were treated intramuscularly with vehicle (saline). The 28-day treatments were followed by a 14-day recovery period (Xu et al. 2020).

Findings From the Repeat-Dose Toxicity Study in Rats

According to the authors, BPC-157 (0.2, 1.0, or 4.0 mg/kg/day, IM, 28 days) had no significant effects on body weights, general behavior, survival, or gross morphology and histopathology of major organs, including heart, liver, kidney, spleen, lung, brain, thymus, prostate, and ovary, in rats (Xu et al. 2020). We note that histopathological data are not included in the manuscript.

Hematological assessments of blood drawn from the rats on post-treatment day 28 and on recovery day 14 revealed statistically significant alterations of mean corpuscular hemoglobin concentration, mean platelet volume index, platelet distribution width, and red blood cell distribution width in BPC-157-treated rats (Table 7). The findings were considered incidental

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[58] 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.

[59] 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.

(i.e., unrelated to the test article) because: (i) the absolute values of the altered parameters remained within the normal ranges for Sprague Dawley rats; (ii) the magnitude of the alterations was small (≤10%), and (iii) the alterations lacked a clear dose-response relationship.

Activated partial thromboplastin time (aPTT) was also found to be slightly, though statistically significantly shorter in male rats treated with BPC-157 doses ≥1 mg/kg/day than in saline-treated male rats (Table 7). The shortening of aPTT, which is a known risk factor for clotting events in humans (Tripodi et al. 2004), appeared to be reversible after discontinuation of treatment (Table 7). The authors considered the shortened aPTT in BPC-157-treated rats to be incidental because, in absolute values, aPTT in these rats remained within the normal range for Sprague Dawley rats.

Table 7. Hematological Effects of 28-Day IM Treatment of Rats With BPC-157.

Animal Sex	BPC-157 dose	Serum Analyte	Treatment day 28	Recovery day 14
Female Rats	1 mg/kg/day	PDW	↔	↓ (8%)*
Female Rats	4 mg/kg/day	PDW	↔	↓ (8%)*
Female Rats	4 mg/kg/day	MCHC	↑ (2%)*	↔
Female Rats	4 mg/kg/day	MPV	↑ (10%)*	↔
Male Rats	4 mg/kg/day	RDW	↔	↓ (7%)*
Male Rats	1 and 4 mg/kg/day	aPTT	↓ (~10%)*	↔

aPTT: activated partial thromboplastin time; MCHC: mean corpuscular hemoglobin concentration; MPV, mean platelet volume index; PDW: platelet distribution width; RDW, red blood cell distribution width; ↑: increased from control; ↓: decreased from control; ↔: unchanged from control. Statistical comparison with control (vehicle-treated rats): *, $p < 0.05$ ANOVA followed by Dunnet. Table generated with data from Xu et al. (2020).

There were statistically significant elevations of triglyceride (TG) levels in the serum of female rats treated with the mid dose of BPC-157 (Table 8). Although serum TG levels were also higher in female rats treated with the low and high doses of BPC-157 than in vehicle-treated female rats, the differences did not appear to reach statistical significance (Table 8). The authors considered the finding to be unrelated to test article in part because serum TG levels in BPC-157-treated female rats remained within the normal levels for Sprague Dawley rats. However, as discussed later (under "*Findings from Repeat-Dose Toxicity Studies in Dogs*"), a similar elevation of serum TG levels was detected among female dogs treated with BPC-157.

Table 8. Effects of 28-Day IM Treatment of Female Rats With BPC-157 on Serum Biochemistry.

BPC-157 dose	Serum analyte	Treatment day 28	Recovery day 14
0.2 mg/kg/day	ALT	↔	↑ (24%)*
0.2 mg/kg/day	Glucose	↔	↑ (31%)*
0.2 mg/kg/day	TG	↑ (37%)	↑ (87%)*

BPC-157 dose	Serum analyte	Treatment day 28	Recovery day 14
1 mg/kg/day	TG	↑ (59%)*	↔
2 mg/kg/day	TG	↑ (31%)	↔

ALT: alanine transaminase; TG: triglycerides; ↑: increased from control; ↓: decreased from control; ↔: unchanged from control. Statistical comparison with control (vehicle-treated rats): *, $p < 0.05$ ANOVA followed by Dunnet. Percentage changes from control that did not reach statistical significance in the study are not accompanied by asterisks. Table generated with data from Xu et al. (2020).

On day 14 after discontinuation of the treatments, serum ALT, glucose, and TG levels were significantly higher in female rats that had been treated with the low dose of BPC-157 than in female rats that had been treated with vehicle (Table 8). The authors interpreted these findings to be incidental (i.e., unrelated to the test article) because the absolute values of the altered parameters remained within the normal ranges for Sprague Dawley rats (Xu et al. 2020).

On recovery day 14, the relative weight of the liver of female rats that had been treated with the low dose of BPC-157 was also significantly (~20%) higher than that of the liver of vehicle-treated female rats. Although the authors attributed the difference in liver weight to food consumption being higher in this group of BPC-157-treated rats than in vehicle-treated female rats, the body weights of BPC-157- and vehicle-treated rats were not different. Therefore, it is unclear whether the liver-related signals detected after 14-day discontinuation of treatment of female rats with the low dose of BPC-157, including the increased serum ALT, glucose, and TG levels and increased relative liver weight, can be definitively interpreted as incidental findings.

Findings From the Repeat-Dose Toxicity Study in Dogs

There were no significant effects of BPC-157 (0.1, 0.5, and 2.0 mg/kg/day, IM, 28 days) on body weights, food consumption, general behavior, survival, or gross morphology and histopathology of major organs, except the liver, in dogs (Xu et al. 2020). Histopathological data are not included in the manuscript.

Treatment of dogs with BPC-157 had no effect on hematological parameters, except aPTT. Specifically, aPTT was longer (by about 20-25%) in male dogs treated for 28 days with BPC-157 doses ≥0.5 mg/kg/day than in saline-treated dogs, with the alteration being statistically significant in dogs treated with the mid dose (0.5 mg/kg/day). On day 14 after discontinuation of treatment, mean aPTT was still longer in dogs treated with BPC-157 doses ≥0.5 mg/kg/day than in saline-treated dogs, but the differences did not reach statistical significance (Xu et al. 2020). Prolonged aPTT can be a risk factor for bleeding events in humans (Santoro et al. 2023).

On post-treatment day 28, BPC-157-treated female dogs presented with statistically significant increases in serum K^+ and TG levels (Table 9). The magnitude of the effects decreased as the BPC-157 doses increased from 0.1 to 2.0 mg/kg/day (Table 9). Male dogs treated with the high dose of BPC-157 (2.0 mg/kg/day) presented with a small, albeit statistically significant reduction of serum glucose levels. These alterations were not detected 14 days after discontinuation of the treatment, suggesting that, if they were test article-related, they were reversible.

Table 9. Effects of 28-Day IM Treatment of Dogs With BPC-157 on Serum Biochemistry.

Animal Sex	BPC-157 dose	Serum analyte	Treatment day 28	Recovery day 14
Female Dogs	0.1 mg/kg/day	K^+	↑ (12%)**	↔
Female Dogs	0.5 mg/kg/day	K^+	↑ (9.5%)*	↔
Female Dogs	2.0 mg/kg/day	K^+	↑ (8.1%)	↔
Female Dogs	0.1 mg/kg/day	TG	↑ (57%)*	↔
Female Dogs	0.5 mg/kg/day	TG	↑ (23%)	↔
Female Dogs	2.0 mg/kg/day	TG	↑ (40%)	↔
Female Dogs	2 mg/kg/day	CREA	↓ (18%)*	↔
Male Dogs	2.0 mg/kg/day	Glucose	↓ (14%)*	↔
Male Dogs	0.1 mg/kg/day	CK	↑ (58%)*	↔
Male Dogs	0.5 mg/kg/day	CREA	↓ (15%)	↔
Male Dogs	2.0 mg/kg/day	CREA	↓ (26%)**	↔

CREA: creatinine; CK: creatine kinase; K^+: potassium; TG: triglycerides. ↑: increased from control; ↓: decreased from control; ↔: unchanged from control. Statistical comparison with control (vehicle-treated rats): **, $p < 0.01$; *, $p < 0.05$ ANOVA followed by Dunnett. Percentage changes from control that did not reach statistical significance in the study are not accompanied by asterisks. Table generated with data from Xu et al. (2020).

Male and female dogs treated with the high dose of BPC-157 (2.0 mg/kg/day) also presented with statistically significant decreases in serum creatinine levels compared to vehicle-treated, sex-matched dogs. In addition, male dogs treated with the mid dose of BPC-157 (0.5 mg/kg/day) presented with mean serum creatinine levels that were lower than those measured in vehicle-treated male dogs, though the effect did not reach statistical significance (Table 9).

The authors interpreted the reduction of serum creatinine levels as an exaggerated pharmacological response of BPC-157. Their interpretation was based on an earlier report that BPC-157-induced muscle healing in rats with muscle injuries was accompanied by a reduction in serum creatine kinase levels (a marker of muscle injury) (Novinscak et al. 2008). However, we note that serum creatine kinase levels in dogs treated with ≥0.5 mg/kg/day BPC-157 were comparable to those measured in control dogs, and the authors did not indicate that the dogs in their study had muscle injuries prior to starting the treatments (Xu et al. 2020).

There were no remarkable differences between the electrocardiographic parameters recorded from BPC-157-treated dogs and vehicle-treated dogs either on post-treatment day 28 or on recovery day 14 (Xu et al. 2020).

The authors concluded that the IM NOAELs for dogs and rats were the highest tested doses of 4 mg/kg and 2 mg/kg, respectively. However, these conclusions should be interpreted with caution because: (i) liver signals (including increased serum ALT, glucose, and TG levels and increased relative liver weight) were noted in female rats after discontinuation of treatment with the low BPC-157 dose (0.2 mg/kg), (ii) serum TG levels were higher in female rats and female dogs

treated with all tested doses of BPC-157 (rats: ≥0.2 mg/kg; dogs: ≥0.1 mg/kg) than in vehicle-treated sex-matched animals, and (iii) serum creatinine levels were significantly lower in female dogs treated with 2 mg/kg BPC-157 and male dogs treated with ≥0.5 mg/kg than in sex-matched, vehicle-treated animals.

At the time of this evaluation, the nominator did not submit, and FDA did not identify nonclinical repeat-dose toxicity studies of BPC-157 (free base) or BPC-157 acetate, delivered via the nominated ROAs (oral, rectal, SC, and nasal).

e. Genotoxicity[60]

The genotoxic potential of BPC-157 (free base) has been assessed in the following tests: (i) bacterial reverse mutation tests (AMES assay) conducted with five Salmonella typhimurium mutant strains (TA97, TA98, TA100, TA102, and TA1535) in the presence and absence of metabolic activation with rat S9 microsomal fraction; (ii) chromosome aberration tests in cultured Chinese hamster lung (CHL) cells in the presence and absence of S9; and (iii) a micronuclei assay conducted with bone marrow harvested from ICR (Institute of Cancer Research) mice that were treated with BPC-157 (25, 50, and 100 mg/kg, IM). For the micronuclei assay, bone marrow was harvested from mice euthanized 24 hours after their treatment and was processed for counting of polychromatic erythrocytes (PCE) micronuclei (Xu et al. 2020).

In the AMES assays, BPC-157 (5 to 2000 µg/plate) did not increase the number of revertant bacterial colonies. In CHL cells, BPC-157 (100 to 400 µg/mL) did not increase the percentage of chromosome aberrations. Finally, BPC-157 (25 to 100 mg/kg, IM) did not increase the percentage of PCE micronuclei in the bone marrow of ICR mice. These findings demonstrate that BPC-157 is not a mutagen (Xu et al. 2020).

f. Developmental and Reproductive Toxicity[61]

The teratogenic potential of BPC-157 has been assessed in pregnant rats treated intramuscularly with vehicle (saline) or BPC-157 (free base; 0.2, 1.0, or 4.0 mg/kg) once a day between gestation

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[60] 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.

[61] 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.

days 6 and 15 (Xu et al. 2020). On gestation day 20, all rats were euthanized, and all fetuses were counted and examined. BPC-157 had no effect on: (i) body weight of the pregnant rats and their fetuses; (ii) numbers of live fetuses, dead fetuses, absorptions, implantations, and corpus luteum; or (iii) total uterine weight or placental weight. In addition, the gestational BPC-157 treatment had no effect on the incidence of fetal malformations. Considering these findings, the IM NOAEL for BPC-157 in pregnant rats is 4.0 mg/kg (Xu et al. 2020).

The article by Xu and colleagues does not describe studies to assess the potential effects of BPC-157 within a complete reproductive cycle, from conception to reproductive capacity in subsequent generations, and to identify the potential effects of BPC-157 on peri- and postnatal development.

At the time of this evaluation, the nominator did not submit, and FDA did not identify developmental and reproductive toxicity studies of BPC-157 (free base) or BPC-157 acetate, delivered via the nominated ROAs (oral, rectal, SC, and nasal). Since the absolute bioavailability of BPC-157 delivered via these routes to rats or dogs is unknown, it is not possible to use the IM NOAEL derived from the teratogenicity study to estimate NOAELs for the nominated ROAs.

g. Carcinogenicity[62]

At the time of this evaluation, the nominator did not submit, and FDA did not identify carcinogenicity studies of BPC-157 (free base) or BPC-157 acetate.

Conclusions: At the time of this evaluation, the nominator submitted, and FDA identified nonclinical pharmacological studies reporting that, in rats, BPC-157-related substances could prevent colonic fistulas, hepatic lesions, and GI lesions induced by different challenges. Researchers have hypothesized that the apparent wound-healing properties of BPC-157-related substances could be related to its ability to up-regulate the expression of growth factors and their receptors, suppress release and/or expression of inflammatory factors, induce angiogenesis, and stimulate nitric oxide synthesis. However, dose-response relationships for BPC-157-related substances to suppress GI and hepatic injuries have not been established, the molecular targets for BPC-157-related substances have not been identified, and the mechanisms of action of BPC-157-related substances remain poorly understood, making it difficult to assess the biological plausibility of the pharmacological effects of BPC-157-related substances.

At the time of this evaluation, FDA identified a published article reporting the results of different nonclinical toxicological studies of BPC-157 (free base). According to the article, BPC-157 (free base) is not a mutagen, and, when delivered via the IM ROA to pregnant rats between gestation days 6 and 15, BPC-157 (free base) does not appear to induce teratogenicity. The article did not include studies assessing potential effects of BPC-157 (free base) within a complete reproductive

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[62] 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.

cycle or on pre-, peri-, and postnatal development. Findings from repeat-dose toxicity studies suggested that 28-day treatment of rats and dogs with BPC-157 (free base) via the IM ROA appeared to be associated with clinically relevant safety signals, including: (i) aPTT shortening and aPTT prolongation (suggestive of altered clotting properties) in rats and dogs, respectively, and (ii) liver-associated signals (increased serum ALT, glucose, and TG levels). Longer lasting repeat-dose toxicity studies were unavailable to demonstrate the reproducibility of the findings and to determine whether additional safety signals emerge with longer treatments. Studies were also unavailable to determine the carcinogenic potential of BPC-157 (free base) or BPC-157 acetate. In addition, the nominator did not submit, and FDA did not identify nonclinical pharmacokinetic and toxicological studies of BPC-157 (free base) or BPC-157 acetate delivered via the nominated ROAs (oral, rectal, transdermal, SC, and nasal). At the time of this evaluation, nonclinical toxicological studies were limited in scope and duration to inform safety considerations for potential clinical uses of BPC-157 (free base) or BPC-157 acetate via the nominated ROAs.

2. Human Safety

The following databases were consulted in the preparation of this section: PubMed, Embase, Cochrane Database of Systematic Reviews, FAERS, Human Foods Program[63] Human Foods Complaint System (HFCS),[64] ClinicalTrials.gov professional healthcare organization websites, and various online clinical references and websites. The clinical articles submitted by the nominators and those identified by FDA do not clearly identify BPC-157 as a free base or salt. Therefore, in this section, the substance will be generally referred to as BPC-157, unless the article under discussion clearly specifies the use of the free base or the acetate salt in a study.

a. Pharmacokinetic Data

Our search of the public medical literature in PubMed and Embase yielded five clinical studies that utilized BPC-157. For the list of references and details of the studies refer to Appendix 1. In two of these studies, authors measured plasma levels of BPC-157 after administration of rectal enemas of BPC-157 (Ruenzi et al. 2005; Veljaca et al. 2002; Veljaca et al. 2003). In both studies, authors report that BPC-157 was not detected in plasma samples. In one abstract (Veljaca et al. 2003), authors state that "most" plasma concentrations of BPC-157 were below the lower limit of quantification of the HPLC-MS/MS (high-performance liquid chromatography coupled with tandem mass spectrometry) assay; but no further details are provided.

We found no human pharmacokinetic data for BPC-157 after oral, SC, nasal, or transdermal administration. We note here that we identified two articles reporting on the in vitro plasma metabolism of BPC-157 for purposes of anti-doping screening (Cox et al. 2017; Tian et al. 2023); however, BPC-157 was not administered to human subjects in these studies.

[63] Formerly Center for Food Safety and Nutrition (CFSAN)
[64] Formerly CFSAN Adverse Event Reporting System (CAERS)

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

The Office of Surveillance and Epidemiology conducted a search of the FAERS database for reports of adverse events (AEs) for BPC-157 through December 4, 2025.[65, 66] The search retrieved three reports.[67] All reports were associated with injectable BPC-157. The reports are summarized below:

- FAERS ID 194222121: A 55-year-old woman reported use of BPC-157 injection compounded by Promise Pharmacy. She reported 9 days of redness and swelling around the injection site; however, she was also using injectable compounded thymosin. Interpretation of the role of BPC-157 in this case is limited by concomitant thymosin injections.
- FAERS ID 23130696: A 28-year-old male reported use of BPC-157 acetate SC injection for "injury/inflammation" compounded by Revive Rx Pharmacy. The patient developed shortness of breath, which resulted in an emergency room visit. No further information was provided (i.e. duration of use, concomitant medications, or temporal relationship to product) which limits interpretation of this AE report.
- FAERS ID 26053573: A 40-year-old female reported using a product containing BPC-157 and TB500 SC twice daily for "joint healing and wound healing support." The product was labeled for "research purposes only" from Cellular Peptide LLC. The patient developed diffuse hyperpigmentation and gingival darkening following initial use of the product containing BPC-157 and TB500 for one week. After two weeks, upon rechallenge with the product, the patient developed identical reproducible reactions. The patient discontinued peptides completely and had no further reactions. The AEs were likely due to the drug product considering that the AEs occurred upon rechallenge; however, because the product contained two peptides it is not possible to assess a potential relationship between BPC-157 and the reported AEs.

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 BPC-157 through December 3, 2025, and retrieved three cases. The assessment of all cases was complicated by use of BPC-157 as part of a multi-ingredient dietary

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[65] The FAERS search did not differentiate between BPC-157 (free base) and BPC-157 acetate.

[66] 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.

[67] It is important to note that FAERS data have limitations. First, there is no certainty that the 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 BPC-157 based on FAERS data alone.

supplement, concurrent medication use, and a lack of details in the report (i.e. duration of use, temporal relationship to product).

We did not identify any case reports associated with BPC-157 published in the literature.

c. Clinical Studies Assessing Safety

Our search of the public medical literature in PubMed and Embase yielded five clinical studies that utilized BPC-157. For the list of references and details of the studies refer to Appendix 1. Based on these studies, BPC-157 has been administered as follows:

- Up to 2 mg/kg rectal enema once daily x 8 days (n=24 healthy subjects)
- 80 mg rectal enema once daily x 2 weeks (approximately 26 subjects with UC)[68]
- 2-4 mg intra-articular injection x 1-2 doses (n=17 subjects with knee pain)
- 10 mg intravesical injection in a single procedure (n=12 subjects with interstitial cystitis)
- 10 mg IV infusion on day 1 and 20 mg IV infusion on day 2 (n=2 healthy subjects)

No serious adverse events appear to have been reported with these studies. However, these studies were of short duration, had small sample sizes, evaluated doses that were likely exploratory in nature, and the authors provided limited information on safety data. Of note, safety monitoring for most of the studies is unclear.[69] Per the meeting abstracts from Veljaca et al. (2002) and Veljaca et al. (2003), the most frequently reported adverse events after BPC-157 administration as an enema to healthy subjects were headache and flatulence.

A search of Clinicaltrials.gov retrieved a single phase 1 study in healthy subjects in Mexico (NCT02637284).[70] Subjects were to receive: 1) Phase 1a- single dose of BPC-157 (1 mg, 3 mg, or 6 mg) or placebo oral tablet by mouth and 2) Phase 1b- BPC-157 3 mg or placebo oral tablet by mouth every 8 hours for two weeks. The estimated enrollment was 42 subjects. There are no results posted, and we were unable to find an associated published study.

d. Other Safety Information (e.g., Relevant Safety Information From Other Regulatory Agencies as Appropriate)

Immunogenicity and Aggregation Concerns

FDA has issued guidance regarding therapeutic protein products.[71] That 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

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[68] Fifty-three subjects were randomized to receive BPC-157 or placebo enema in a 1:1 fashion. The number of subjects randomized to the BPC-157 group is not provided in the abstract.
[69] Lee and Burgess (2025) provide some details of safety monitoring in their study in two healthy subjects.
[70] We searched https://clinicaltrials.gov/ on 12/3/2025 using the search terms "BPC-157" and "Bepecin".
[71] See FDA's guidance for industry. *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014) available at https://www.fda.gov/media/85017/download.

protein products, the concerns about immunogenicity are also relevant to peptides (such as BPC-157), which can similarly elicit an immunogenic response; this immunogenic response may be enhanced when peptides are given via SC or nasal ROA. In general, SC and nasal ROA is associated with increased immunogenicity compared to oral or rectal 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 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 we did not identify any studies that formally investigated the immunogenicity of BPC-157 products. As a peptide with 15 amino acids that is administered through a parenteral or nasal ROA, BPC-157 may pose a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities, as discussed above. In addition, peptides administered through the rectal or transdermal ROA may have the potential for immunogenicity depending on the administration environment. Lastly, although inherent immunogenic risk for BPC-157 administered orally is likely to be low, FDA is concerned about the other risks related to peptides described above, such as the potential for peptide-related impurities which may impact the safety of the product in other ways. The nomination did not include, and FDA is not aware of, information about BPC-157 to suggest that this substance does 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 that proposed for the BPC-157 compounded drug product(s).[72] Please see Section II.C.c for more information about alternative approved therapies.

Conclusions: There is insufficient clinical safety information to characterize the safety profile of BPC-157 (free base) and BPC-157 acetate. We found no studies that administered BPC-157 to

[72] 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.

humans via the proposed oral, SC, nasal, or transdermal ROA. We identified two studies that administered BPC-157 as a rectal enema to either healthy subjects or subjects with UC for a maximum of two weeks. No serious adverse events were reported in these studies; however, the authors provided limited information on safety and associated safety monitoring. UC is a chronic condition which may need long-term repeated treatment. There is insufficient information to support patient safety for the long-term use of BPC-157 in patients with UC. There is no information to assess the pharmacokinetics of BPC-157 in humans; however, it does not appear that BPC-157 is absorbed systemically when given as a rectal enema.

Adverse events in the FAERS database for BPC-157 included the following: injection site reaction, shortness of breath, and diffuse hyperpigmentation and gingival darkening. However, it is unclear whether these AEs were attributable to BPC-157. FDA's ability to interpret FAERS reports is limited by lack of information in the reports and confounding factors such as the use of concomitant medications.

The safety profile of compounded drug products containing BPC-157 can be negatively impacted by various factors that include but are not limited to the product formulation, peptide concentration, and conditions of storage favoring the generation of product-related impurities and/or peptide aggregates capable of inducing untoward immunogenic responses. As a peptide with 15 amino acids that is administered through a parenteral or nasal ROA, BPC-157 may pose a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities. In addition, peptides administered through the rectal or transdermal ROA may have the potential for immunogenicity depending on the administration environment. The nomination did not include, and FDA is not aware of, information about BPC-157 to suggest that this substance does not present these risks. At the time of this evaluation, there are several FDA-approved drug products indicated to treat UC.

III. CONCLUSION AND RECOMMENDATION

We have balanced the criteria described in section II above to evaluate BPC-157 (free base) and BPC-157 acetate for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs against*** BPC-157 (free base) and BPC-157 acetate being placed on that list based on the following:

1. Conclusions on the physical and chemical characterization for each BPC-157-related BDS, BPC-157 (free base) and BPC-157 acetate, are included in subsections 1.1 and 1.2, respectively.

   1.1.

   BPC-157 (free base) is reported to be a pentadecapeptide fragment of BPC. As reported in the literature, BPC-157 is expected to be stable under storage conditions below -18°C.

   BPC-157 (free base) is considered not well-characterized from the physical and chemical characterization perspective based on (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., USAN, INN, IUPAC), and (2) data/information relevant to certain CQAs for establishing its identity, purity, and quality for its intended use in the proposed dosage forms were either lacking or deemed to be inadequate

in the nomination packages or not found in the publicly available scientific literature. For example, some of this data/information include but are not limited to testing for CQAs relevant to characterizing peptide-related impurities and aggregates, microbial quality (bioburden, bacterial endotoxins), particle size, or other CQAs as dictated by dosage form (e.g., injection, metered-dose spray solution, capsule, topical cream, suppository) and ROA (SC injection, transdermal, nasal, oral, rectal). Additionally, FDA would have strong concerns about the use of this BDS in the proposed compounded nasal spray solution product due to lack of information about the container closure system (including container, closure, pump) – all of which are relevant to the CQAs for the proposed product and would affect how the BDS is delivered via this product.

Further, FDA is concerned about the potential for immunogenicity of BPC-157 (free base) when formulated in an injectable dosage form due to the potential for aggregation as well as potential peptide-related impurities, as discussed in the *Likely Impurities* section II.A.1.c. We also note that the stability, pharmacological activity, and immunogenic properties of peptides are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

1.2.

BPC-157 acetate is reported to be a salt of BPC-157 (free base) peptide of fifteen amino acids. As reported in the literature, BPC-157 acetate is expected to be stable under reported storage conditions below -20°C.

BPC-157 acetate is considered not well-characterized from the physical and chemical characterization perspective based on (1) inconsistent naming conventions that do not follow established chemical nomenclature standards (e.g., USAN, INN, IUPAC), and (2) data/information relevant to certain CQAs for establishing its identity, purity, and quality for its intended use in the proposed dosage forms were either lacking or deemed to be inadequate in the nomination packages or not found in the publicly available scientific literature. For example, some of this data/information include but are not limited to testing for CQAs relevant to characterizing peptide-related impurities and aggregates, microbial quality (bioburden, bacterial endotoxins), particle size, or other CQAs as dictated by dosage form (e.g., injection, metered-dose spray solution, capsule, topical cream, suppository) and ROA (SC injection, transdermal, nasal, oral, rectal). Additionally, FDA would have strong concerns about the use of this BDS in the proposed compounded nasal spray solution product due to lack of information about the container closure system (including container, closure, pump)– all of which are relevant to the CQAs for the proposed product and would affect how the BDS is delivered via this product.

Further, FDA is concerned about the potential for immunogenicity of BPC-157 acetate when formulated in an injectable dosage form due to the potential for aggregation as well as potential peptide-related impurities, as discussed in the *Likely Impurities* section II.A.1.c. We also note that the stability, pharmacological activity, and immunogenic properties of peptides are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

2. As previously mentioned, it is often unclear whether the BPC-157 discussed in the sources considered for this section is the salt formulation or the free base. Therefore, FDA considered the information discussed for both the free base and salt form. BPC-157 was first described in the literature in 1993 and was referred to as a possible endogenous free radical scavenger and organoprotection mediator. Interstitial cystitis, knee pain, and UC are the uses of BPC-157-related BDSs examined in the literature. GI uses are the most commonly mentioned uses listed on websites. BPC-157-related BDSs are marketed as an oral capsule, oral spray, nasal spray, and injectable product. However, it is unclear whether some of these products are compounded or if pharmacies are currently compounding products containing BPC-157-related BDSs. There is no approved product containing BPC-157-related BDSs in any country at this time, nor is BPC-157 (free base) or BPC-157 acetate found in the European, Japanese, or the International Pharmacopeias. Currently available data and published literature is too limited for FDA to understand the historical use of BPC-157 (free base) and BPC-157 acetate in compounded drug products.

3. There is a lack of evidence to support the effectiveness of BPC-157 (free base) and BPC-157 acetate as a treatment for UC. There has been a single, small trial evaluating BPC-157 in the treatment of UC, however, interpretation of the results is limited by the lack of details provided in the meeting abstract and the exploratory nature of the study. We did not identify any studies that administered BPC-157 via the oral, SC, nasal, or transdermal ROA in subjects with UC. At the time of this evaluation, the data available do not support the use of BPC-157 for the treatment of UC. There are multiple FDA-approved drug products indicated to treat UC, a serious chronic disease that may cause life-threatening complications.

4. Nonclinical pharmacological studies have reported that BPC-157-related substances could prevent colonic fistulas, hepatic lesions, and GI lesions induced by different challenges in rats. However, it is difficult to assess the biological plausibility of these pharmacological effects because dose-response relationships for BPC-157 (free base) and BPC-157 acetate to suppress GI and hepatic injuries have not been established, the molecular targets for BPC-157-related substances have not been identified, and the mechanisms of action of BPC-157-related substances remain poorly understood. At the time of this evaluation, nonclinical toxicological studies were also too limited in scope and duration to inform safety considerations for potential clinical uses of BPC-157 (free base) or BPC-157 acetate via the nominated oral, rectal, transdermal, SC, and nasal ROAs.

   There is insufficient clinical safety information to characterize the safety profile of BPC-157 (free base) and BPC-157 acetate. We found no studies that administered BPC-157 to humans via the proposed oral, SC, nasal, or transdermal ROA. We identified two studies that administered BPC-157 as a rectal enema to either healthy subjects or subjects with UC for a maximum of two weeks. No serious adverse events were reported in these studies; however, the authors provided limited information on safety and associated safety monitoring. UC is a chronic condition which may need long-term repeated treatment. There is insufficient information to support patient safety for the long-term use of BPC-157 in patients with UC. There is no information to assess the pharmacokinetics of BPC-157 in humans; however, it does not appear that BPC-157 is absorbed systemically when given as a rectal enema.

Adverse events in the FAERS database for BPC-157 included the following: injection site reaction, shortness of breath, and diffuse hyperpigmentation and gingival darkening. However, it is unclear whether these AEs were attributable to BPC-157. FDA's ability to interpret FAERS reports is limited by lack of information in the reports and confounding factors such as the use of concomitant medications.

The safety profile of compounded drug products containing BPC-157 can be negatively impacted by various factors that include, but are not limited to the product formulation, peptide concentration, and conditions of storage favoring the generation of product-related impurities and/or peptide aggregates capable of inducing untoward immunogenic responses. As a peptide with 15 amino acids that is administered through a parenteral or nasal ROA, BPC-157 may pose a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities. In addition, peptides administered through the rectal or transdermal ROA may have the potential for immunogenicity depending on the administration environment. The nomination did not include, and FDA is not aware of, information about BPC-157 to suggest that this substance does not present these risks. At the time of this evaluation, there are several FDA-approved drug products indicated to treat UC.

On balance, the physicochemical characterization, information on historical use, lack of evidence of effectiveness, and safety information identified for both BPC-157 (free base) and BPC-157 acetate weigh against them being added to the 503A Bulks List. In particular, FDA's proposal is based on the fact that BPC-157 (free base) and BPC-157 acetate are not well characterized from a physiochemical perspective, there is a lack of information on the safety profile and immunogenicity risks of BPC-157-related BDSs, there is insufficient evidence to make a conclusion on the effectiveness of BPC-157-related BDSs as a treatment for UC, and there are FDA-approved drug products that are indicated to treat UC, a serious chronic disease that may cause life-threatening complications. Accordingly, we propose not adding BPC-157 (free base) or BPC-157 acetate to the 503A Bulks List.

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V. APPENDIX

APPENDIX 1: PREVIOUS HUMAN EXPERIENCE WITH BPC-157.

Reference	Study type	Subjects (N)	BPC-157 treatment	Safety findings
Veljaca et al. 2002; Veljaca 2003	Placebo-controlled phase 1 tolerability and PK study (meeting abstracts)	Healthy subjects (N=32 randomized; N=24 received BPC-157)	BPC-157 0.25, 0.5, 1, and 2 mg/kg or placebo enema. Each dose group consisted of 6 subjects treated with BPC-157 and 2 subjects treated with placebo. Each subject received a single dose followed by a one-week washout period and an additional seven doses, once daily for seven days.	"Physical examination, observation of clinical signs as well as laboratory testing have revealed no significant adverse events that could be attributed to single and repeated seven-day treatment with PL 14736." “The most frequently reported adverse events, headache and flatulence, occurred with no obvious difference in frequency or severity after PL 14736 and placebo dosing.”
Ruenzi et al. 2005	Multicenter, randomized, double-blind, placebo-controlled study (meeting abstract)	Subjects with mild to moderate UC (N=53 randomized; 46 completed study)	Randomized in a 1:1 ratio to receive BPC-157 enema 80 mg or placebo once daily x 2 weeks.	"PL 14736 was very well tolerated and safe. There was no difference in the frequency or type of adverse events in comparison with placebo."
Lee and Padgett 2021	Retrospective chart review at the Institute for Hormonal Balance in Orlando, FL	Subjects with knee pain (N=17 identified; 16 contacted by investigators)	Intra-articular injection of BPC-157* alone or combined with thymosin-beta-4 (TB4). Dose of BPC-157 ranged from 2-4 mg (1-2 doses).	“This peptide was well tolerated with no adverse events noted.”

Reference	Study type	Subjects (N)	BPC-157 treatment	Safety findings
Lee et al. 2024	Single arm study at UroGyn Specialists of Florida clinic	Subjects with moderate to severe interstitial cystitis (N=12 women)	Intravesical injections of 1 mg BPC-157** placed in 10 spots (total of 10 mg) in the uroepithelium of the bladder wall.	"No one dropped out of the study, and no adverse events were reported" "None of the participants experienced symptoms of fever, skin rash, nausea or vomiting, irritative urinary symptoms (urgency or frequency), or dyspareunia. No postprocedural complications of hematuria or acute cystitis were reported."
Lee and Burgess 2025	Single arm study at the Institute for Hormonal Balance in Florida	"Healthy" subjects (N=2)	Day 1: BPC-157** 10 mg IV infused over 1 hour. Day 2: BPC-157** 20 mg IV infused over 1 hour.	No AEs reported (subjects asked about AEs at visits/day 1, 2, and 3). Authors did not report any clinically significant changes in vital signs (BP or HR) or laboratory values (CMP, CBC, CPK with isozymes, BNP, TSH, RBC magnesium, CRP).

*BPC-157 was compounded by Tailor Made Compounding in Nicholasville, KY.
**BPC-157 was compounded by 503A compounding pharmacy in the United States that did not wish to disclose its name.
Abbreviations: BNP = B-type natriuretic peptide; BP = blood pressure; CBC = complete blood count; CMP = comprehensive metabolic panel; CPK (creatinine phosphokinase); CRP = C-reactive protein; HR = heart rate; PK = pharmacokinetic; RBC = red blood cell; TSH = thyroid stimulating hormone.

BPC-157 – Related Bulk Drug Substances (BPC-157 (free base) and BPC-157 acetate) Nominations

International Peptide Society Submission for Docket No. FDA-2013-N-1525: Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug and Cosmetic Act; Revised Request for Nominations	
Ingredient Name	BPC-157
Is it a "bulk drug substance"	Yes
Is it listed in the Orange Book	No
Does it have a USP or NF Monograph	No
Chemical Name	H-Gly-Glu-Pro-Pro-Pro-Gly-DL-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val-OH
Common Name(s)	BPC157, BPC 157, Bepecin, PL-10, PL-14736, PLD-116
UNII Code	8ED8NXK95P
Chemical Grade	Provided by FDA Registered Supplier/COA
Strength, Quality, Stability, and Purity	Assay, Description, Solubility, etc.; Example of Integrative Medical Group Certificate of Analysis for this chemical is attached.
How supplied	Lyophilized Powder
Recognition in foreign pharmcopeias or registered in other countries	HALMED approval
Submitted to USP for monograph consideration	Yes
Compounded Dosage Forms	Oral capsules, Subcutaneous Injectable, Transdermal Cream
Compounded Strengths	500 mcg/capsule, 2,000 mcg/ml
Anticipated Routes of Administration	Oral capsules, Subcutaneous Injectable, Transdermal Cream
Saftey & Efficacy Data	Jelovac, N. et al., 1998. A novel pentadecapeptide, BPC 157, blocks the stereotypy produced acutely by amphetamine and the development of haloperidol-induced supersensitivity to amphetamine. Biological Psychiatry, 43(7), 511–519. http://dx.doi.org/10.1016/s0006-3223(97)00277-1.
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Used Previously to compound drug products	Yes
Proposed use	Ulcerative colitis, Crohn's disease, Celiac disease, Tendonitis
Reason for use over and FDA-approved product	no FDA-approved product available
Other relevant information - Stability information	Added as an attachment

INTEGRATIVE MEDICAL GROUP

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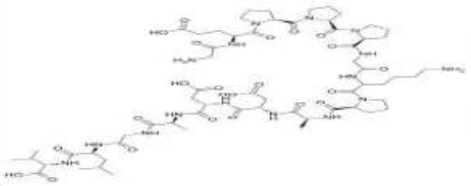
Certificate of Analysis

Cat#:	Product Name:	Lot#:
BPC	BPC-157 (Acetate Salt)	22218-BPC-A

Chemical name	
Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val	
Synonyms	
Body Protection Compound-157 BPC-157 Acetate Salt	
Chemical structure	**CAS# and Theoretical analysis**
	Name: BPC-157 CAS#: 137525-51-0 Lot#: 22218-BPC-A Chemical Formula: $C_{62}H_{98}N_{16}O_{22}$ Exact Mass: 1419.53552 Molecular Weight: 1419.56

Analysis item	Specifications / Results
Appearance	White to off-white powder
Structure	^{1}H-NMR analysis matches the structure. MS analysis gives the correct molecule weight. Both NMR and MS data are consistent with those reported in the literature.
Purity (HPLC)	98.34%
Solubility	Soluble in water.
Conclusion	This product conforms with IMG's quality standards
Shipping condition	Shipped under ambient temperature as non-hazardous chemical. This product is stable for a few weeks during ordinary shipping and time spent in customs.
Storage condition	Short term storage (weeks): 0 – 4 °C under dry condition Long term storage (months): -20 °C under dry condition
Shelf life	2 years if properly stored.

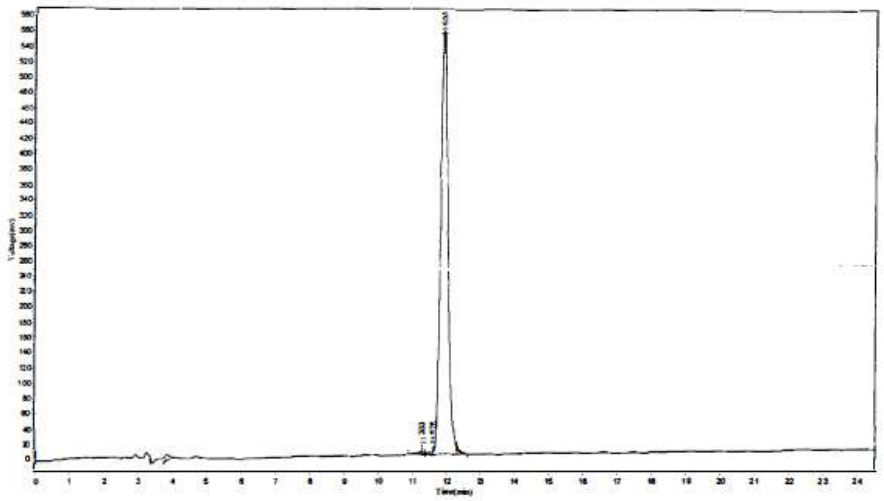
Prepared and Checked by:
Charles Sullivan (QA/QC) Ch Sullv

Date: 8/11/18

Structure:BPC-157(acetate Salt) BPC-A
Lot NO :22218-BPC-A
Number :0200049
Column :250*4.6mm,Kromasil-C18-5um
Solvent A:0.1%TFA in 100%water
Solvent B:0.1%TFA in 100%acetonitrile

Gradient :	A	B
0.1min	85%	15%
25.0min	60%	40%
25.1min	0%	100%
30.0min	stop	

Flow rate:1.0ml/min
Wavelength(nm):220
Volume :10ul



Peak No.	Ret Time	Height	Area	Conc.
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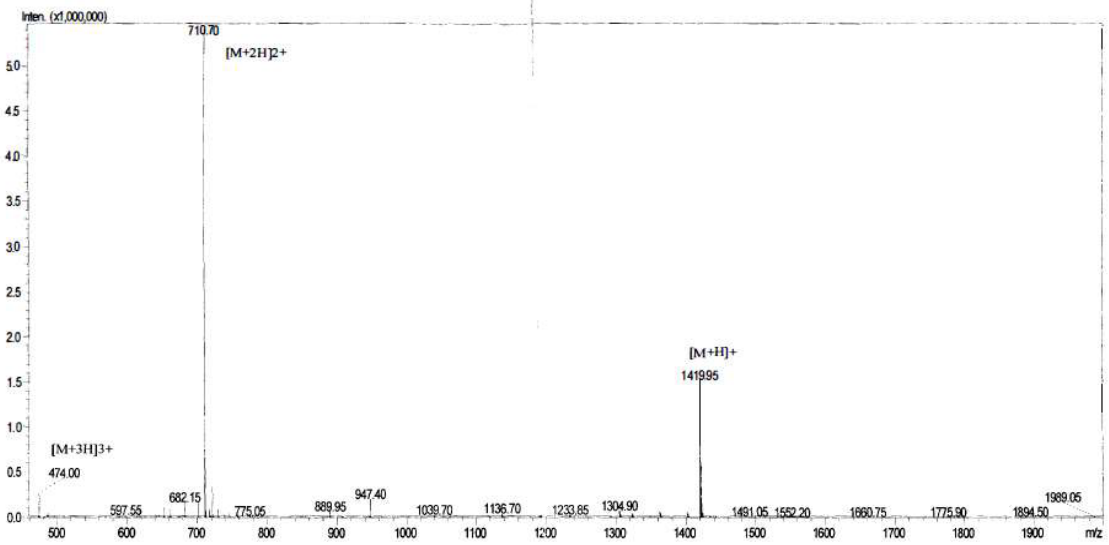
2	11.628	3615.962	34462.469	0.4225
3	11.880	553672.125	8030367.000	98.4386
4	11.880	11418.524	51932.746	0.6366
Total				100.00

MS Spectrum



Acquired by :Chas Sullivan
Data Acquired : 2018/8/11
Injection Volume : 1
Sample Name : BPC-157(acetate Salt) BPC-A
Mw : 1419.53
Lot No. : 22218-BPC-A

Probe	:ESI	Probe bias	:+4.5kv
Nebulizer Gas Floe	:1.5L/min	Detector	:1.2kv
CDL	:-20.0v	T.Flow	:0.2ml/min
CDL Temp	:250℃	B.conc	:50%H2O/50%ACN
Block Temp	:400℃		

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?	BPC-157
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**: (4S)-4-[(2-Aminoacetyl)amino]-5-[(2S)-2-[(2S)-2-[(2S)-2-[[2-[[6-amino-1-[(2S)-2-[[(2S)-1-[[(2S)-3-carboxy-1-[[(2S)-3-carboxy-1-[[(2S)-1-[[2-[[(2S)-1-[[(1S)-1-carboxy-2-methylpropyl]amino]-4-methyl-1-oxopentan-2-yl]amino]-2-oxoethyl]amino]-1-oxopropan-2-yl]amino]-1-oxopropan-2-yl]amino]-1-oxopropan-2-yl]amino]-1-oxopropan-2-yl]carbamoyl]pyrrolidin-1-yl]-1-oxohexan-2-yl]amino]-2-oxoethyl]carbamoyl]pyrrolidine-1-carbonyl]pyrrolidine-1-carbonyl]pyrrolidin-1-yl]-5-oxopentanoic acid • **Sequence**: H-Gly-Glu-Pro-Pro-Pro-Gly-DL-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val-OH • **IUPAC**: glycyl-L-alpha-glutamyl-L-prolyl-L-prolyl-L-prolyl-glycyl-DL-lysyl-L-prolyl-L-alanyl-L-alpha-aspartyl-L-alpha-aspartyl-L-alanyl-glycyl-L-leucyl-L-valine
What is the common name of the substance?	BPC-157, Bepecin, Body Protection Compound, PL-10, PL-14736, PLD-116
Does the substance have a UNII code?	8ED8NXK95P
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?	Purity: >95% Refrigerated or Freezer Stable Specifications and Example of Pharmaceutical 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?	HALMED approval

Has information been submitted about the substance to the USP for consideration of drug monograph development?	YES
What dosage form(s) will be compounded using the bulk drug substance?	• Oral capsules • Subcutaneous Injection • Nasal Spray Solution • Rectal Suppository
What strength(s) will be compounded from the nominated substance?	• Capsule: 250mcg, 500 mcg, 1mg • Injection: 2,000 mcg/mL • Nasal Spray: 50mcg/spray (500mcg/mL) • Suppository: 1mg/each
What is the anticipated route(s) of administration of the compounded drug product(s)?	See Above
Are there safety and efficacy data on compounded drugs using the nominated substance?	• Sikiric P. The pharmacological properties of the novel peptide BPC 157 (PL-10). *Inflammopharmacology*. 1999;7(1):1-14. doi:10.1007/s10787-999-0022-z • Seiwerth S, Sikiric P, Grabarevic Z, et al. BPC 157's effect on healing. *Journal of Physiology-Paris* 91(3-5) 1997: 173-178. ISSN 0928-4257 https://doi.org/10.1016/S0928-4257(97)89480-6. • Gwyer D, Wragg NM, Wilson SL. Gastric pentadecapeptide body protection compound BPC 157 and its role in accelerating musculoskeletal soft tissue healing. Cell Tissue Res. 2019;377(2):153-159. doi:10.1007/s00441-019-03016-8 • Gaginella TS. Clinical relevance of basic research in peptic ulcer disease. *J Gastroenterol Hepatol*. 1994;9 Suppl 1:S99-S103. doi:10.1111/j.1440-1746.1994.tb01311.x • Huang T, Zhang K, Sun L, et al. Body protective compound-157 enhances alkali-burn wound healing in vivo and promotes proliferation, migration, and angiogenesis in vitro. *Drug Des Devel Ther*. 2015;9:2485-2499. Published 2015 Apr 30. doi:10.2147/DDDT.S82030 • Filaretova LP, Takeuchi K (eds): Cell/Tissue Injury and Cytoprotection/Organoprotection in the Gastrointestinal Tract: Mechanisms, Prevention and Treatment. *Front Gastrointest Res*. Basel, Karger, 2012, vol 30, pp 191–201 DOI:10.1159/000338435 • Sikiric P, Seiwerth S, Rucman R, et al. Brain-gut Axis and Pentadecapeptide BPC 157: Theoretical and Practical Implications. *Curr Neuropharmacol*. 2016;14(8):857-865. doi:10.2174/1570159x13666160502153022 • Chang CH, Tsai WC, Hsu YH, Pang JH. Pentadecapeptide BPC

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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?	Ulcerative colitis, Crohn's disease, Celiac disease, Tendonitis
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

DARMERICA

Certificate of Analysis

BPC-157 Acetate

Product Name : BPC-157 Acetate
Mfg. Date : May 12, 2020
M.F. : $C_{62}H_{98}N_{16}O_{22}$
CAS No. : 137525-51-0
Sequence : H-Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val-OH

Lot No. : DL5241
Exp. Date : May 11, 2022
M.W. : 1419.54
Batch Qty : 264.590 g

TESTS	SPECIFICATIONS		RESULTS
Appearance	White or off-white powder		White powder
Identification	Molecular Ion Mass (by ESI)	1419.5 ± 1.0	1419.7
Related Substance (HPLC)	Maximum individual impurity	≤ 3.0%	1.1%
	Total impurities	≤ 5.0%	2.2%
Acetic Acid	≤ 3.0%		0.37%
Purity (HPLC)	≥ 95.0%		97.8%

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

Note: Analytical results transcribed from the original COA provided by Zhejiang Apeloa Pharmaceuticals Co., Ltd.; Lot No.:DL5241205002

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

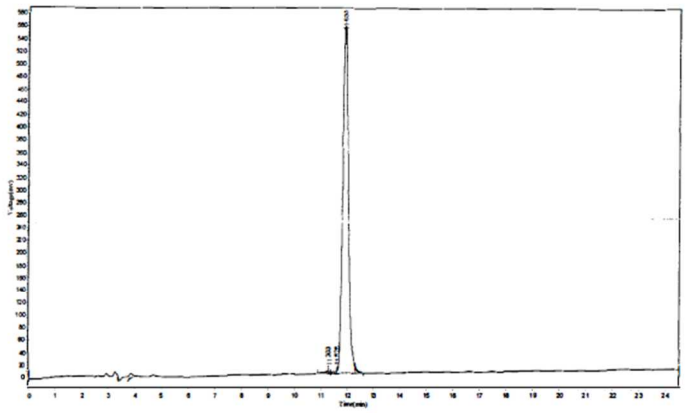
	Name	Title	Signature	Date
Prepared by	Wilnelia Hernandez	Quality Assistant	WHR	06/15/2020
Released by	Sai Rasane	Quality Assistant		06/15/2020

4/28/2020
no change needed

Structure:BPC-157(acetate Salt) BPC-A
Lot NO :22218-BPC-A
Number :0200049
Column :250*4.6mm,Kromasil-C18-5um
Solvent A:0.1%TFA in 100%water
Solvent B:0.1%TFA in 100%acetonitrile

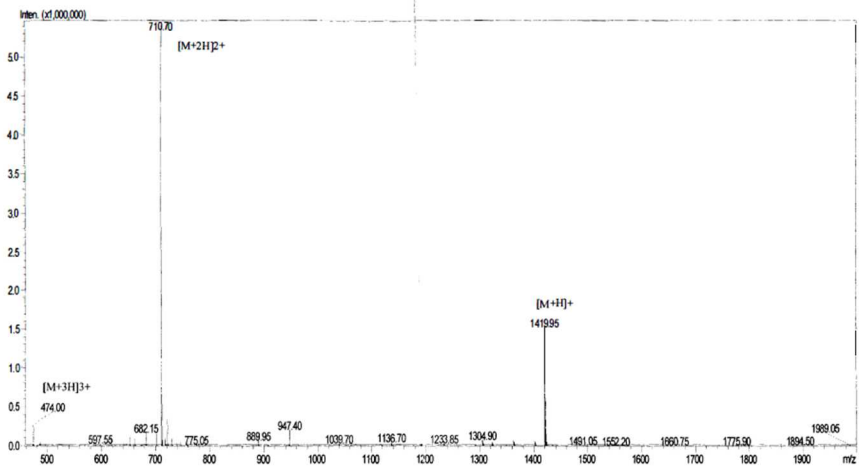
Gradient :	A	B
0.1min	85%	15%
25.0min	60%	40%
25.1min	0%	100%
30.0min	stop	

Flow rate:1.0ml/min
Wavelength(nm):220
Volume :10ul



Peak No.	Ret Time	Height	Area	Conc.
1	11.303	2588.601	40980.598	0.5024
2	11.628	3615.962	34462.469	0.4225
3	11.880	553672.125	8030367.000	98.4386
4	11.880	11418.524	51932.746	0.6366
Total				100.00

MS Spectrum



Acquired by :Chas Sullivan
Data Acquired : 2018/8/11
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