FDA Introductory Remarks

Pharmacy Compounding Advisory Committee Meeting

July 23, 2026

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Compounding Basics

- Compounded Drug Products
  - Are not FDA-approved, meaning they are not reviewed by FDA for safety, efficacy, or manufacturing quality before marketing
  - Can serve an important role for patients whose medical needs cannot be met by an FDA-approved drug product but at times have been associated with adverse events specific to the quality of the compounded drug product
  - Under 503A are primarily overseen by state regulators

503A Evaluation Process

- FDA evaluates:
  - Information provided by the nominator: proposed use(s), including any relevant peer-reviewed medical literature submitted in support of the proposed use(s)
  - Additional use(s) that are widespread, for serious conditions, or that pose serious risks to patients, as needed
  - Publicly available information from published medical literature, clinical guidelines, various databases/websites, etc.
- FDA assesses each substance according to four criteria:
  1. Physical and chemical characterization
  2. Safety issues raised by use in compounded products
  3. Available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance
  4. Historical use in compounded products

503A Evaluation Process

- Multidisciplinary evaluation team:
  - Office of Compounding Quality and Compliance
  - Office of New Drugs
  - Office of Pharmaceutical Quality

When a BDS is placed on the 503A Bulks List:

1. The compounded drug product is not FDA approved
2. A drug product compounded under Section 503A is not required to have a label to inform patients and providers how to use it
3. The compounded drug product is not required to comply with current good manufacturing practice however, the prohibition on insanitary conditions still applies
4. Compounders operating under section 503A are not required to report adverse events associated with compounded drug products to the FDA
5. Unless specific limitations are included on the entry, the bulk drug substance (BDS) can be compounded for any use or via any route of administration (dosage form)

Real World Evidence

- Real-world evidence:
  - The clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world data
  - Sources of real-world data can be analyzed in non-interventional studies, including registries, electronic health records (EHRs), and medical claims
  - Information on dispensing or patient use is not the same thing as real-world data or clinical evidence about the usage and potential benefits or risks of a medical product

Other Pathways for Study and Use

- Expanded Access Investigational New Drug Application
    - Presents opportunity to access an investigational medical product for patients with a serious or immediately life-threatening disease or condition who have no comparable or satisfactory alternative therapies
    - Goal is access for treatment use
- Clinical Trial under an Investigational New Drug Application
    - Provide necessary data to determine safety and effectiveness
    - Most efficient path to market and broad availability
    - Goal is research about the drug potentially leading to approval
- Not a consideration in determining whether a bulk drug substance is appropriate for inclusion on the 503A Bulks List

Orphan Drug Designation

- Orphan Drug Designation
  - Designation as an orphan drug is a separate process from seeking FDA approval or licensure
  - A request for orphan drug designation must include a discussion of the scientific rationale to establish a medically plausible basis for the use of the drug for the rare disease or condition
  - Drugs for rare diseases must still go through the same rigorous scientific review process as any other drug for approval or licensing
  - The process for evaluating bulk drug substances for inclusion on the 503A Bulks List is also a separate process from seeking FDA approval or licensure, but the considerations differ from those for orphan drug designation

July 23, 2026 PCAC Bulk Drug Substances

- July 23, 2026
  - BPC-157-related BDSs (BPC-157 (free base) and BPC-157 acetate)
  - KPV-related BDSs (KPV (free base) and KPV acetate)
  - TB-500-related BDSs (TB-500 (free base) and TB-500 acetate)
  - MOTS-c-related BDSs (MOTS-c (free base) and MOTS-c acetate)

FDA's Human Drug Compounding Website

Human Drug Compounding

Drug Compounding

Compounding is generally a practice in which a licensed pharmacist, a licensed physician or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes or alters ingredients of a drug to create a medication tailored to the needs of an individual patient.

Compounded drugs are not FDA approved, which means the agency does not review their safety, effectiveness or quality before they are marketed. Although compounded drugs can serve an important medical need for certain patients, they also may pose risks to patients.

FDA's compounding program aims to protect patients from poor-quality compounded drugs, while preserving access to lawfully-marketed compounded drugs for patients who have a medical need for them.

Email us: compounding@fda.hhs.gov

Sign up for compounding and Compounding Quality Center of Excellence emails

Find information on FDA's compounding oversight and compliance actions

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Pharmacy Compounding Advisory Committee: Bulk Drug Substance (BDS) Discussion of Conflated Bulks and Common Name Challenges July 23 and 24, 2026

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Disclosure

- **This speaker has no conflicts of interest to disclose**

Rationale and Objectives

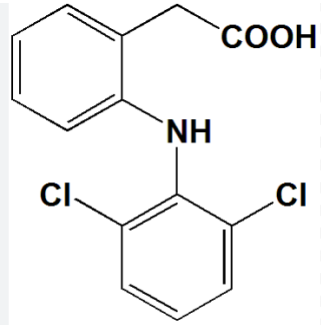
- In an evaluation(s) presented today, FDA will discuss multiple “related” but distinct bulk drug substances (BDSs) conflated in compounding nomination submissions
- We are also encountering significant challenges associated with the use of common or company names
- This is concerning because its not clear what is being nominated, compounded, or what substance patients are being dosed with
- Goals of this presentation
  - Discuss regulatory definitions for BDS, active pharmaceutical ingredient (API) and active moiety (AM) and how BDS differences have implications for the drug products made with them
  - Discuss challenges with company and common name BDS lacking United States Adopted Names Council (USAN)

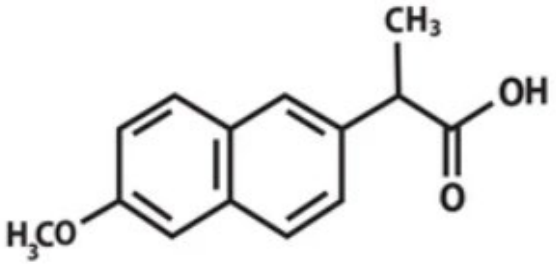
There Are Often Different BDS Forms…

- **Different salt and ester forms, as well as different active moiety**

- Diclofenac	- Naproxen
- Diclofenac Epolamine	- Naproxen Sodium
- Diclofenac Sodium	
- Diclofenac Potassium	

How many distinct BDSs and Active Moieties?





BDS/API Forms – Why Do They Exist?

- **The specific form of API used in a formulated product is typically chosen for its physical, chemical, or pharmacokinetic-pharmacodynamic (PK/PD) characteristics which renders it more suitable for drug product processing**
- **The selection can be dosage form-specific due to unique critical quality attributes (CQAs) associated with a dosage form**
- **Each of those forms is a distinct BDS under the FD&C Act**

Statute and Regulations

- **Per 21 CFR 207.3, a BDS is the same as an Active Pharmaceutical Ingredient (API):**

  "*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."

- **API is defined in FDA regulations at 21 CFR 207.1:**

  "*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."

What is an Active Moiety?

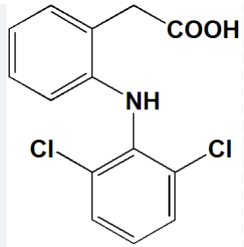
- **An active moiety is defined at 21 CFR 314.3:**

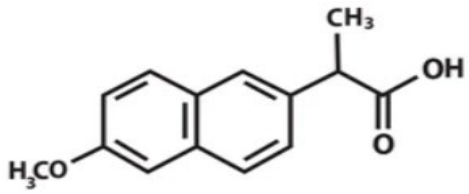
  "*Active moiety* means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the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

Two Active Moieties and Six BDS

- Diclofenac	- Naproxen
- Diclofenac Epolamine	- Naproxen Sodium
- Diclofenac Sodium	
- Diclofenac Potassium	

All NSAIDs
6 Distinct BDSs
2 Active Moieties





Each of those 6 forms above is a distinct BDS and API under the FD&C Act

Why Does This Matter From Regulatory Perspective?

When FDA places a BDS on the 503A Bulks List through rulemaking, and a salt or ester of an active moiety is listed, only that particular salt or ester may be used.

The base compound and other salts or esters of the same active moiety must be evaluated for eligibility.

See, for example, 81 FR 91071.

Why Does This Matter From Patient's Perspective?

- Different salts, esters and the free base can have very different properties and toxicities
  - Physicochemical properties
    - Chemical formula/Molecular weight
    - Solid state stability
    - Solution stability
    - Solubility
    - Polymorphism
  - Pharmacology/Toxicology profile
  - PK/PD profile

- These definitions and distinctions are as important in compounding as they are in drug product manufacturing. This is not just a matter of regulations or definitions; this is a critical matter scientifically as these different forms have different chemical structures as well as different physical, chemical, PK/PD characteristics. This can impact patient safety and product efficacy.

Challenges with Unique Identifiers and Databases

- Global Substance Registration System (GSRS)
  - Used by multiple worldwide regulatory agencies
  - Home of the Unique Ingredient Identifier (UNII)

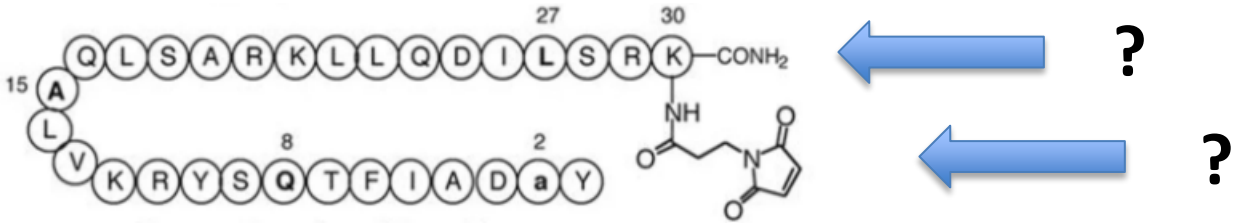
- Chemical Abstracts Services (CAS)
  - Home of unique identifier known as CAS Registry Number (CAS RN)

- Manufacturers/suppliers populate these databases
  - They provide structure and related information
  - Regulators do not own or police the data contained therein

Company and Common Name Challenges, and USAN

- Common or company names often used for experimental substances have no meaning
  - New forms are frequently synthesized as part of drug discovery process to mitigate toxicities or improve efficacy or other properties

- Multiple forms and derivatives of experimental substances do exist and might be sold under the same name
  - CJC-1295 for example



- This naming/identity problem is unique to the intersection of experimental substances and compounding
  - While not a consideration in determining whether a bulk drug substance is appropriate for inclusion on the 503A Bulks List, the Investigational New Drug (IND) pathway helps to address this problem and provides patient access
    - Compounders can avail themselves to this pathway
  - USAN (or similar naming conventions) also addresses this issue

Physical and Chemical Characterization

- **[For] physical and chemical characterization of the substance, FDA would consider each substance's purity, identity, and quality. Based on attributes such as the substance's molecular structure, stability, melting point, appearance, likely impurities, and solubilities, FDA would determine whether the substance can be identified consistently based on its physical and chemical characteristics. If a substance cannot be well characterized chemically and physically, the Agency proposes that this *criterion weigh against its inclusion […] because there can be no assurance that its properties and toxicities, when used in compounding, would be the same as the properties and toxicities reported in the literature and considered by the Agency*." *Emphasis added*.**
  - **2016 Proposed Rule, Docket No. FDA-2016-N-3464.**
  - **See 81 FR 91071**

Conclusion

- BDS is defined as the same as an API in the regulations and each distinct form is a distinct BDS each with unique physical, chemical and PK/PD characteristics which can impact patient safety and product efficacy
  - Our physical chemical characterization assessment and conclusion is specific to each unique BDS
- Nominators, BDS Manufacturers, and Compounders need to be aware of which single BDS is nominated, manufactured, and used to formulate a compounded product
- UNII and CAS# databases are not controlled by FDA
- Common and company names are highly problematic for experimental substances
  - USAN are useful to clearly identify for compounders, providers, and patients a specific substance
  - While not a consideration in determining whether a bulk drug substance is appropriate for inclusion on the 503A Bulks List, establishing an IND to evaluate a substance of interest can provide patient access to a specified, well-characterized substance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BPC-157-related Bulk Drug Substances: BPC-157 (Free Base) and BPC-157 Acetate

Pharmacy Compounding Advisory Committee Meeting

July 23, 2026

Center for Drug Evaluation and Research (CDER)
U. S. Food & Drug Administration (FDA)

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Special Thanks to: **Division of Gastroenterology (DG)**

Introduction

- Body Protection Compound-157 (BPC-157)-related bulk drug substances (BDSs) were nominated for inclusion on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (503A Bulks List)
  - BPC-157 (free base)
  - BPC-157 acetate

- There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for BPC-157 (free base) or its acetate form

- Neither is a component of an FDA-approved drug

Evaluation

- BPC-157-related bulk drug substances (BDSs) were evaluated for treatment of ulcerative colitis (UC)
- Proposed drug products:
  - Capsule: 250 µg, 500 µg, and 1 mg, oral
  - Injection: 2,000 µg/mL, subcutaneous (SC)
  - Nasal spray solution: 50 µg/spray (500 µg/mL)
  - Suppository: 1 mg, rectal
  - Transdermal cream
- The nominations were withdrawn, and FDA is evaluating these substances at its discretion

Evaluation Criteria

- Physical and chemical characterization
- Available evidence of effectiveness or lack of effectiveness
- Safety concerns
- Historical use in compounding

BDS Nomenclature

- BPC-157 is a common name and not a USAN, INN, or IUPAC name
- FDA has encountered multiple salts, and derivatives, including different active moieties, sold commercially under the same common name
  - Inconsistent naming conventions can contribute to the BDS being not well-characterized
- USAN program and naming convention exist to ensure that the patient is provided with the drug the prescriber intended

USAN: United States Adopted Name
INN: International Non-proprietary Name
IUPAC: International Union of Pure and Applied Chemistry

Summary of Basic Information on BPC-157 Free Base and BPC-157 Acetate

	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	$C_{62}H_{98}N_{16}O_{22}\cdot X(C_2H_4O_2)$/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	Yes	Yes
Active Moiety	BPC-157 (free base)	BPC-157 (free base)

UNII: Unique Ingredient Identifier; CAS = Chemical Abstracts Service; MF = molecular formula; MW = molecular weight

Summary of Information Submitted in Two Withdrawn Nominations

Nominator	Nomination 1	Nomination 2
Nominated BDS	BPC-157	BPC-157
BDS per UNII code	8ED8NXK95P *(matches BPC-157 free base)*	8ED8NXK95P *(matches BPC-157 free base)*
Certificate of Analysis (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 (g/mol)	1,419.54 *(provided in the CoA, matches BPC-157 free base)*	1,419.54 *(provided in the CoA, matches BPC-157 free base)*
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 Subcutaneous Injection 2,000 µg/mL Nasal Spray Solution 50 µg/spray (500 µg/mL) Rectal Suppository 1 mg/each	Oral capsules 500 µg/capsule Subcutaneous Injectable 2,000 µg/mL Transdermal Cream

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

Critical Quality Attributes (CQA) for Nominated Dosage Forms

- Injection/SC injection: bioburden load (i.e., microbial enumeration test), bacterial endotoxins test (BET), and solubility
- Oral capsule: particle size distribution, and microbial test
- Transdermal cream, rectal suppository: particle size (for suspended solid BDS), microbial limit
- Metered-dose nasal spray solution products:
  - The container closure system (CCS) including container, closure, and pump are considered critical components of metered-dose nasal spray solution products CQAs for nasal spray device: pump delivery, spray content uniformity, spray pattern and plume geometry, and droplet size distribution
  - Nasal spray solution: Microbial quality, suitability/compatibility of the device components with the formulation, and solubility of the BDS

Physical and Chemical Characterization (1)

BPC-157 acetate

- BPC-157 acetate is reported to be an acetate salt of the BPC-157 (free base), a pentadecapeptide fragment of BPC (H-Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val-OH)
- White to off-white powder, soluble in water at 5 mg/mL
- Has no USP drug substance monograph
- BDS storage and stability:
  - Manufacturer recommends storing in sealed container at 2°C to 8°C, or -20°C under dry conditions
  - Can be sensitive to product formulation, process, and environmental conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (2)

- Potential Impurities:
  - Peptide-related impurities: due to incomplete coupling reactions, truncations, or side reactions; peptide-related aggregates
  - Peptide synthesis process-related impurities: impurities in the protected amino acid starting materials (e.g., isomeric impurities, free amino acids), residual solvents, coupling reagents, activators, catalysts, and scavengers
- In the CoA provided:
  - No information regarding the nature of individual impurities. Such information was also not found in publicly available scientific literature
  - Lack of information on the potential of peptide aggregation
  - Lack of microbial bioburden and/or bacterial endotoxin tests
- Potential for immunogenicity:
  - Associated with the impurities and peptide related aggregates, especially when formulated in an injectable or nasal dosage form

Physical and Chemical Characterization (3)

Conclusion: BPC-157 acetate is not well-characterized.

- Inconsistent naming conventions that do not follow established chemical nomenclature standards
- Lack of certain critical characterization data (impurities, aggregates, bioburden, and bacterial endotoxins)
- Potential for immunogenicity when formulated in an injectable or nasal spray dosage form due to potential for aggregation as well as peptide-related impurities
- Lack of information on critical attributes associated with other proposed pharmaceutical dosage forms such as transdermal cream, oral capsule, and rectal suppository
- Lack of information about the CCS for metered-dose spray solution, including container, closer, and pump – all of which are relevant to the CQAs for the proposed product and would affect how the BDS is delivered via this product

Physical and Chemical Characterization (4)

BPC-157 (Free Base)

- Pentadecapeptide fragment of BPC (H-Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val-OH)
- White to off-white powder, soluble in water at 5 mg/mL
- Has no USP drug substance monograph
- BDS storage and stability:
  - Manufacturer recommends storing in desiccated containers below -18°C
  - Can be sensitive to product formulation, process, and environmental conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (5)

- Potential Impurities:
  - Peptide-related impurities: due to incomplete coupling reactions, truncations, or side reactions; peptide-related aggregates
  - Peptide synthesis process-related impurities (e.g., isomeric impurities, free amino acids, starting materials, residual solvents, coupling reagents, activators, catalysts, and scavengers)

- No CoA for BPC-157 (free base) in the nomination

- CoA found from public domain (related to CQAs control):
  - No information on impurity limits/testing results
  - Lack of information on the potential of peptide aggregation
  - Lack of microbial bioburden and/or BET

- Potential for immunogenicity:
  - Associated with the impurities and peptide related aggregates, especially when formulated in an injectable or nasal dosage form

Physical and Chemical Characterization (6)

Conclusion: BPC-157 (free base) is not well-characterized.

- Inconsistent naming conventions that do not follow established chemical nomenclature standards
- Lack of certain critical characterization data (impurities, aggregates, bioburden, and bacterial endotoxins)
- Potential for immunogenicity when formulated in an injectable or nasal spray dosage form due to potential for aggregation as well as peptide-related impurities
- Lack of information on critical attributes associated with other proposed pharmaceutical dosage forms such as transdermal cream, oral capsule, and rectal suppository
- Lack of information about the CCS for metered-dose spray solution, including container, closer, and pump – all of which are relevant to the CQAs for the proposed product and would affect how the BDS is delivered via this product

BPC-157 (Free Base) or BPC-157 Acetate

- The references reviewed do not clearly identify whether the substance discussed is BPC-157 (free base) or BPC-157 acetate
- In the next sections, the substances will be generally referred to as BPC-157

Pharmacology

- In nonclinical pharmacological studies, BPC-157-related BDSs prevented colonic fistulas, hepatic lesions, and gastric lesions induced by different challenges in rats
  - Researchers hypothesize that the observed effects of BPC-157-related BDSs in the gastrointestinal (GI) system may be related to up-regulation of the expression of growth factors and their receptors, suppression of release/expression of inflammatory factors, induction of angiogenesis, and/or stimulation of nitric oxide synthesis

- <u>Limitations of Pharmacological Studies</u>:
  - Dose-response relationships for BPC-157-related BDSs to mitigate GI lesions have not been established
  - Pharmacological studies have been limited to rodent models
  - The molecular targets for BPC-157 have not been identified, and the mechanisms of action of BPC-157 are unknown

Pharmacokinetics

Nonclinical:

- After a single intravenous (IV) dose of BPC-157 (free base), BPC-157 half-life was 5.3 min in Beagle dogs and 15.2 min in Sprague Dawley rats (He et al. 2022)
- Intramuscular (IM) bioavailability was ~18% in rats and ~39% in dogs (He et al. 2022)
- In rats, radiolabeled BPC-157 administered IM was quickly metabolized into shorter peptide fragments, and elimination was mainly via the urine and feces (He et al. 2022)
- The pharmacokinetic (PK) profiles of BPC-157 delivered via the nominated routes of administration (ROAs) (oral, rectal, SC, nasal, transdermal) are unknown at this time

Clinical:

- BPC-157 was not detected in plasma samples after rectal (enema) administration of BPC-157 in two studies (Ruenzi et al. 2005; Veljaca et al. 2002/Veljaca et al. 2003)
- The PK profiles of BPC-157 delivered via the nominated ROAs (oral, SC, nasal, transdermal) are unknown at this time

Overview of UC

- UC is a form of inflammatory bowel disease (IBD)
- UC involves inflammation of the rectum that may extend in a continuous fashion to more proximal portions of the colon
- 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
- Guidelines for the management of UC (American College of Gastroenterology and American Gastroenterological Association) do not mention BPC-157
- UC is a serious chronic disease. Patients who do not receive effective treatment are at a greater risk for both short-term complications (e.g., severe bleeding, bowel perforation) and long-term complications (e.g., colon cancer)

Treatment of UC

- Overall goals:
  - Reduce signs and symptoms of active disease
  - Decrease the underlying mucosal inflammation
  - Prevent short- and long-term complications
- The choice of therapy is guided by the disease severity, extent of disease, and presence of other manifestations (e.g., extraintestinal complications, malabsorption)
- There are several FDA-approved drug products that are indicated to treat UC
  - Conventional therapies: oral and rectal aminosalicylates; immunomodulators; intravenous, oral, and rectal corticosteroids
  - Therapeutic biologic products: tumor necrosis factor (TNF) blockers, anti-integrin agents, and interleukin inhibitors
  - Targeted small molecule therapies: janus kinase (JAK) inhibitors and sphingosine-1-phosphate (S1P) receptor modulators

Clinical Effectiveness – Clinical Studies

Ruenzi et al. 2005 (meeting abstract):

- Multicenter, randomized, double blind, placebo-controlled study in 53 subjects with mild to moderate UC who received BPC-157 rectal enema 80 mg or placebo once daily x 2 weeks
- Mean change in the Disease Activity Index (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
  - DAI was "a composite score of clinical, laboratory, endoscopic, and pathohistological findings"

Limitations: Details lacking, including but not limited to information regarding the primary endpoint (e.g., DAI), inclusion/exclusion criteria, statistical methods, and post-treatment follow-up

Clinical Effectiveness – Conclusion

- Lack of evidence to support the effectiveness of BPC-157 (free base) and BPC-157 acetate as a treatment for UC
- 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
- FDA did not identify any studies that administered BPC-157 via the oral, SC, nasal, or transdermal ROA in subjects with UC
- There are multiple FDA-approved drug products indicated to treat UC

Nonclinical - Safety (1)

- Repeat-dose toxicity studies (Xu et al. 2020)
  - 28-day treatment of rats and dogs with BPC-157 (free base) via the IM ROA was associated with statistically significant safety signals that are potentially clinically relevant
    - Coagulopathy-related signals:
      - ↓Activated partial thromboplastin time (aPTT) in rats (at doses ≥1 mg/kg/day) and ↑aPTT in dogs (at doses ≥0.5 mg/kg/day)
    - Potentially liver-associated signals:
      - ↑Serum levels of triglyceride (TG) during treatment of female rats with ≥0.2 mg/kg/day and female dogs with ≥0.1 mg/kg/day
      - ↑Serum levels of TG, alanine aminotransferase (ALT), and glucose and ↑relative liver weight on day 14 after end of treatment of female rats with 0.2 mg/kg/day
      - ↓Serum creatinine levels in female dogs at 2 mg/kg/day

Nonclinical - Safety (2)

- Genotoxicity studies (Xu et al. 2020)
  - BPC-157 (free base) was not genotoxic in in-vitro and in-vivo assays

- Developmental and reproductive toxicity studies (Xu et al. 2020)
  - Once daily IM injections of BPC-157 (free base, up to 4 mg/kg/day) in rats between gestation days 6 and 15 induced no fetal malformation and had no effect on fetal viability
  - The nominator did not submit, and FDA did not identify, studies assessing potential effects of BPC-157 (free base) or BPC-157 acetate within a complete reproductive cycle or on peri- and postnatal development

Nonclinical - Conclusion

- Repeat-dose toxicity studies suggest that 28-day treatment of rats and dogs with BPC-157 (free base) via the IM ROA was associated with clinically relevant safety signals potentially related to coagulopathy and the liver
  - Longer lasting repeat-dose toxicity studies were unavailable to demonstrate whether these safety signals persist, or additional signals emerge with chronic exposure to BPC-157-related BDSs
- The nominator did not submit, and FDA did not identify, nonclinical PK and toxicological studies of BPC-157 (free base) or BPC-157 acetate delivered via the nominated ROAs
- 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

Clinical Safety - FAERS

- Retrieved *three* adverse event (AE) reports:
  - A 55-year-old woman reported use of BPC-157 injection [ROA not specified] compounded by Promise Pharmacy. She reported 9 days of redness and swelling around the injection site; however, she was also using injectable compounded thymosin
  - 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
  - A 40-year-old female reported use of BPC-157 and TB500 SC twice daily for “joint healing and wound healing support.” The patient had diffuse hyperpigmentation and gingival darkening which were reproducible upon rechallenge
- Unclear if these AEs were attributable to BPC-157. FDA’s ability to interpret FAERS reports is limited by lack of information and confounding factors (e.g., concomitant medications)

FAERS data have limitations. Reporting is voluntary. FDA does not receive all AE reports that may potentially occur with a product, especially for compounded products

Clinical Safety - Clinical Studies

- BPC-157 has been administered in clinical studies 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)
  - 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)
- Authors provided limited safety data, and safety monitoring in most studies is unclear; no serious AEs appear to have been reported
- Studies were of short duration, had small sample sizes, and evaluated doses that were likely exploratory in nature
- Per the meeting abstracts from Veljaca et al. (2002 and 2003), the most frequently reported AEs after BPC-157 administration as an enema to healthy subjects were headache and flatulence

Clinical Safety - Immunogenicity Concerns

- BPC-157 is reported to be a 15-amino acid peptide
- Peptides may elicit an immunogenic response; this response may be enhanced when peptides are given via the SC and nasal ROA
- BPC-157 may pose a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities
  - 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

Clinical Safety - Conclusion

- There is insufficient clinical safety information to characterize the safety profile of BPC-157 (free base) and BPC-157 acetate
- FDA found no studies that administered BPC-157 to humans via the proposed oral, SC, nasal, or transdermal ROA
- No serious AEs were reported in studies that administered BPC-157 as a rectal enema; however, 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 long-term use of BPC-157 in patients with UC
- As a peptide with 15 amino acids that is administered through a parenteral or nasal route of administration, BPC-157 may pose a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities
- There are several FDA-approved drug products indicated to treat UC

Historical Use in Compounding (1)

- The nominator did not provide historical use data; however, the literature shows that BPC-157 was first described in 1993
  - Insufficient information available to determine how long BPC-157-related BDSs have been used in pharmacy compounding

- Studies identified in the published literature describe the use of compounded drug products containing BPC-157-related BDS for knee pain, interstitial cystitis, and UC

- A FAERS (FDA Adverse Events Reporting System) case report indicated that a compounded BPC-157 acetate product (SC injection) was used for “inflammation and injury”

- No outsourcing facility has reported compounding drug products containing BPC-157-related BDSs to FDA

Historical Use in Compounding (2)

- Drug products containing BPC-157-related BDS appear to be offered online:
  - Variety of uses, including for GI uses and to accelerate the healing of injuries and wounds
  - As an oral capsule, oral spray, nasal spray, and injectable product
- BPC-157 is not a component of an approved product in any country, nor is it found in the European, Japanese, or International Pharmacopeias
- Listed on the World Anti-Doping Agency's prohibited list under the non-approved substances (S0) section

Historical Use in Compounding (3)

Conclusion: Internet search results indicate that websites appear to offer drug products containing BPC-157-related BDSs in various formulations for a variety of uses; however, it is unclear whether some of these products are compounded or if pharmacies are currently compounding products containing BPC-157-related BDSs. Currently available data and published literature are too limited for FDA to understand the historical use of BPC-157 (free base) and BPC-157 acetate in compounded drug products

Evaluation Conclusion

A balancing of the criteria weighs against BPC-157 (free base) or BPC-157 acetate being placed on the 503A Bulks List

FDA's conclusion is based on the facts that these substances:

- Are not well characterized from a physicochemical perspective
- Have limited information on the historical use in compounding
- Lack information on the safety profile and immunogenicity risks
- Have insufficient evidence to make a conclusion on the effectiveness of BPC-157-related BDSs as a treatment for UC, and there are currently FDA-approved therapies for the management of UC, a serious chronic disease that may cause life-threatening complications

Recommendation

FDA is proposing that BPC-157 (free base) and BPC-157 acetate NOT be included on the 503A Bulks List.


FDA
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ADMINISTRATION

KPV-related Bulk Drug Substances: KPV (Free Base) and KPV Acetate

Pharmacy Compounding Advisory Committee Meeting

July 23, 2026

Center for Drug Evaluation and Research (CDER)
U.S. Food & Drug Administration (FDA)

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Special Thanks to: **Office of New Drugs - Division of Dermatology and Dentistry**

Introduction

- KPV-related bulk drug substances (BDSs) were nominated for inclusion on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (503A Bulks List)
  - KPV (free base)
  - KPV acetate

- There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for KPV (free base) or its acetate form

- Neither is a component of an FDA-approved drug

Nomination

- KPV-related BDSs were evaluated for the following uses:

  "Wound healing, Inflammatory conditions (psoriasis, eczema, etc.)"

- Drug products proposed:
  Cream and gel, 0.1% for topical administration

- The nomination was withdrawn, and FDA is evaluating these substances at its discretion

Evaluation Criteria

- Physical and chemical characterization
- Available evidence of effectiveness or lack of effectiveness
- Safety concerns
- Historical use in compounding

BDS Nomenclature

- KPV is a common name and not a USAN, INN, or IUPAC name

- FDA has encountered multiple salts and derivatives, including different active moieties, being marketed under the same common name
    - Inconsistent naming conventions can contribute to a potential safety risk for patients

- USAN program and other naming conventions exist to ensure that the patient is provided with the drug the prescriber intended

USAN: United States Adopted Name
INN: International Non-proprietary Name
IUPAC: International Union of Pure and Applied Chemistry

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

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

CAS: Chemical Abstracts Service; MF: molecular formula; MW: molecular weight

Summary of Information Submitted in the Withdrawn Nomination

Nominator	Nomination 1
Nominated BDS	KPV
BDS per UNII code	Not available
CoA	CoA provided for KPV Acetate
CAS No.	67727-97-3 (*matches KPV free base*)
MF	$C_{16}H_{30}N_4O_4$ (*provided in the nomination package/CoA that matches KPV free base*)
MW (g/mol)	Not provided
Chemical Name	(2S)-2-[[(2S)-1-[(2S)-2,6-diaminohexanoyl]pyrrolidine-2-carbonyl]amino]-3-methylbutanoic acid (*matches KPV free base*)
Proposed Products	0.1% cream and gel for topical administration

Italics in the table above represents the information identified by the FDA.
CoA: Certificate of Analysis

Physical and Chemical Characterization (1)

KPV (Free Base)

- A tripeptide composed of the amino acids Lysine (K), Proline (P), and Valine (V)
- White to off-white lyophilized powder. Soluble in water up to 0.7 mg/mL as reported
- Has no USP drug substance monograph
- BDS storage and stability:
  - It is recommended to be stored in a tightly closed container, stable up to 3 years when stored at -20 °C, up to 2 years at 4°C, and up to 3 months at 15°C
  - Can be sensitive to product formulation, manufacturing processes, and environmental conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (2)

- Potential general impurities for peptide:
  - Peptide-related impurities: due to incomplete coupling reactions, truncations, or side reactions; peptide-related aggregates
    - Peptide synthesis process-related impurities: impurities in the protected amino acid starting materials (e.g., isomeric impurities, free amino acids), residual solvents, coupling reagents, activators, catalysts, and scavengers

- No CoA provided in the nomination

- CoAs found from public domain:
  - No information on impurity limits/testing results
  - Lack of information on the potential of peptide aggregation
  - Lack of microbial testing

Physical and Chemical Characterization (3)

Conclusion: KPV (free base) is considered not well-characterized:

- Inconsistent naming conventions that do not follow established chemical nomenclature standards
- Lack of certain critical characterization data associated with proposed dosage forms of KPV (free base), including impurities, aggregates, and microbial testing
- Lack of information on the formulation of proposed cream/gel final products, FDA cannot evaluate how the physical and chemical characteristics, particularly limited water solubility (0.7 mg/mL) and particle size, impact the performance of final products

Physical and Chemical Characterization (4)

KPV Acetate

- Acetate salt of KPV, composed of Lysine (K), Proline (P), and Valine (V)
- White to off-white powder. Soluble in water at 5 mg/mL
- Has no USP drug substance monograph
- BDS storage and stability:
  - Long-term storage conditions: In a sealed container at 2°C to 8°C recommended in the CoA the nominator provided
  - Can be sensitive to product formulation, manufacturing processes, and environmental conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (5)

- Potential general impurities for peptide:
  - Peptide-related impurities: due to incomplete coupling reactions, truncations, or side reactions; peptide-related aggregates
  - Peptide synthesis process-related impurities: impurities in the protected amino acid starting materials (e.g., isomeric impurities, free amino acids), residual solvents, coupling reagents, activators, catalysts, and scavengers

- In the CoA submitted:
  - No information on the nature of single impurity
  - Lack of information on the potential of peptide aggregation
  - Lack of microbial testing
  - FDA was unable to identify such information in the publicly available scientific literature

Physical and Chemical Characterization (6)

Conclusion: KPV acetate is considered not well-characterized:

- Inconsistent naming conventions that do not follow established chemical nomenclature standards
- Lack of certain critical characterization data associated with the proposed dosage forms of KPV acetate, including the nature of single impurity, potential peptide related aggregates, as well as microbial testing data
- Due to lack of information on the formulation of proposed cream/gel final products, FDA cannot evaluate how the physical and chemical characteristics, such as particle size, impact the performance of final products

KPV (Free Base) or KPV Acetate

- The references reviewed do not clearly identify whether the substance discussed is the KPV (free base) or KPV acetate
- In the next sections, the substances will be generally referred to as KPV

General Pharmacology

- KPV is reported to be a synthetic tripeptide (L-lysine-L-proline-L-valine) that corresponds to the amino acid sequence 11 through 13 of the endogenous melanotropic peptide α-MSH (melanocyte stimulating hormone)
- In nonclinical pharmacological studies, KPV presented anti-inflammatory properties but lacked the melanotropic activity of α-MSH
- KPV does not appear to interact with the melanocortin receptors that mediate the pharmacological effects of α-MSH. The molecular targets of KPV are unknown.
- The anti-inflammatory properties of KPV may be related to:
  - KPV-induced inhibition of nuclear factor-κB activation leading to a reduction in the expression of proinflammatory cytokines, and
  - KPV-induced inhibition of the effects of proinflammatory cytokines such as interleukin 1β

Pharmacokinetics

- According to an in-vitro study conducted in human cadaver skin, KPV does not permeate well through skin
  - The low skin permeability of KPV could limit the systemic toxicity of KPV applied topically to the skin
  - However, it could also limit the potential effectiveness of KPV as a topical therapeutic agent because it could prevent the penetration of KPV through the stratum corneum into the lower layers of the epidermis
- At the time of this evaluation, the nominator did not submit, and FDA did not identify, clinical studies in humans assessing pharmacokinetics, nonclinical pharmacokinetic or toxicokinetic studies of KPV (free base) or KPV acetate

Clinical Effectiveness

- The nominator listed the proposed uses: “Wound healing” and “Inflammatory Conditions (psoriasis, eczema, etc.)”
  - Wounds and inflammatory conditions can be serious of life-threatening
  - There are currently various FDA-approved therapies with established efficacy for the management of wounds and various inflammatory diseases including for psoriasis and eczema

- The nominator did not provide clinical evidence on the use of KPV in wound healing or inflammatory conditions

- FDA performed a search of published medical literature and FDA did not identify data, such as clinical studies, on the use of KPV in humans

Conclusion: There is a lack of evidence to evaluate the effectiveness of KPV for the nominated uses

Nonclinical Safety

At the time of this evaluation, the nominator did not submit, and FDA did not identify, nonclinical toxicity studies to inform safety considerations for potential clinical uses of KPV (free base) or KPV acetate applied topically to the skin

Clinical Safety (1)

- FDA Adverse Event Reporting System (FAERS):
  - Search retrieved no adverse event (AE) reports for KPV[1]

- Human Food Program (HFP) Human Foods Complaint System (HFCS)
  - Search retrieved no reports for KPV

[1] Note the lack of reports for KPV does not imply that the substance is safe or lacks toxicities. FAERS data have limitations. Reporting is voluntary. FDA does not receive all AE reports that may potentially occur with a product, especially for compounded products

Clinical Safety (2)

- The nomination did not include, and FDA has not identified, any clinical studies or human exposure data for KPV via any route of administration

- Potential safety risks associated with the use of KPV in humans are unknown

- KPV is a peptide reportedly containing 3 amino acids. The nominators did not provide, and FDA did not identify, clinical studies or human exposure data assessing immunogenicity or aggregation of KPV

Safety - Conclusion

- There is lack of clinical and nonclinical safety information on the use of KPV (free base) and KPV acetate
- FDA is concerned about the lack of human data on drug products containing KPV administered via any route of administration, including lack of information to assess immunogenic safety risks
- Potential safety risks associated with the use in humans are unknown
- There are currently available FDA-approved therapies for the management of wounds and to treat various inflammatory diseases

Historical Use in Compounding (1)

- The earliest use and extent of KPV use in compounding is unknown
- No evidence of compounded drug products containing KPV in the published literature or in outsourcing facility reports
- Compounded drug products containing KPV appear to be offered online in the United States:
  - As single and multiple-peptide injectable, oral, topical, and nasal spray drug products
  - For use in conditions such as inflammation, inflammatory bowel diseases, wound healing, nerve damage, stroke, gut health, and psoriasis
- KPV (free base) and KPV acetate are not recognized in the European Medicines Agency website, European or Japanese Pharmacopoeias

Historical Use in Compounding (2)

Conclusion: The extent to which KPV-related BDSs have been used in compounding is unknown. Published literature did not reveal studies in which compounded drug products containing KPV-related BDSs were used in humans. Internet search results indicate that websites appear to offer drug products containing KPV-related BDSs in various formulations for a variety of uses.

Evaluation Conclusion

- A balancing of the criteria weighs against KPV (free base) or KPV acetate being placed on the 503A Bulks List
- FDA's conclusion is based on:
  - These substances are not well-characterized from a physical and chemical characterization perspective
  - Extent of use of KPV-related BDS in compounding is unknown
  - Lack of information on their use when administered in humans to make a conclusion on their clinical safety and effectiveness
- There are currently FDA-approved therapies for the management of wounds and for the treatment of various inflammatory diseases

Recommendation

FDA is proposing that KPV (free base) and KPV acetate NOT be included on the 503A Bulks List


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TB-500-related Bulk Drug Substances: TB-500 (Free Base) and TB-500 Acetate

Pharmacy Compounding Advisory Committee Meeting

July 23, 2026

Center for Drug Evaluation and Research (CDER)
U.S. Food & Drug Administration (FDA)

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Special Thanks to: **Office of New Drugs – Division of Dermatology and Dentistry**

Introduction

- TB-500-related bulk drug substances (BDSs) were nominated for inclusion on the list of BDSs that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (503A Bulks List)
  - TB-500 (free base)
  - TB-500 acetate
- There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for TB-500 (free base) or its acetate form
- Neither is a component of an FDA-approved drug

Evaluation

- TB-500-related BDSs were evaluated for treatment of:
  - Wound healing
- Proposed product:
  - 3 mg/mL lyophilized powder for subcutaneous (SC) and intramuscular (IM) injection
- The nomination was withdrawn, and FDA is evaluating these substances at its discretion

Evaluation Criteria

- Physical and chemical characterization
- Available evidence of effectiveness or lack of effectiveness
- Safety concerns
- Historical use in compounding

BDS Nomenclature

- TB-500 is a common name and not a USAN, INN, or IUPAC name
- FDA has encountered multiple salts, and derivatives, including different active moieties, sold commercially under the same common name
  - Inconsistent naming conventions can contribute to a potential safety risk for patients
- USAN program and other naming conventions exist to ensure that the patient is provided with the drug the prescriber intended

USAN: United States Adopted Name
INN: International Non-proprietary Name
IUPAC: International Union of Pure and Applied Chemistry

Summary of Basic Information on TB-500 (Free Base) and TB-500 Acetate

	TB-500 (free base)	TB-500 Acetate
UNII Code	QHK6Z47GTG	Not available
CAS No.	885340-08-9	Not available
MF/MW (g/mol)	$C_{38}H_{68}N_{10}O_{14}$/889.01	$C_{38}H_{68}N_{10}O_{14}\cdot CH_3COOH$/949.1
Peptide sequence	Ac-Leu-Lys-Lys-Thr-Glu-Thr-Gln-OH	Ac-Leu-Lys-Lys-Thr-Glu-Thr-Gln-OH.CH_3CO_2H
Supplier	Yes	Yes
Active Moiety	TB-500 (free base)	TB-500 (free base)

UNII: Unique Ingredient Identifier; CAS: Chemical Abstracts Service; MF: molecular formula; MW: molecular weight

Summary of Information Submitted in the Withdrawn Nomination

Nominator	Nomination 1
Nominated BDS	TB-500 (free base)
BDS per UNII code	QHK6Z47GTG (*matches TB-500 free base*)
CoA	CoA provided for TB-500 Acetate
CAS No.	885340-08-9 *(matches TB-500 free base) ("AKA CAS # 476014-70-7" provided in the nomination package matches neither TB-500 free base nor TB-500 acetate)*
MF	$C_{38}H_{66}N_{10}O_{14}$ *(provided in the nomination package, matches neither TB-500 free base nor TB-500 acetate, Molecular Formula provided in the CoA is not legible)*
MW	889.01 *(provided in the CoA, matches TB-500 free base)*
Chemical Name	Ac-Leu-Lys-Lys-Thr-Glu-Thr-Gln-OH (*matches TB-500 free base*)
Proposed Products	SC / IM Injectable, 3 mg/mL

Italics in the table above represents the information identified by the FDA.
CoA: Certificate of Analysis

Critical Quality Attributes (CQAs) for Nominated Dosage Form

SC/IM Injection

- Bioburden load (i.e., Microbial enumeration test)
- Bacterial Endotoxins Test (BET)
- Solubility

Physical and Chemical Characterization (1)

TB-500 (Free Base)

- A seven amino acid synthetic fragment of thymosin β4 and an acetyl group at the N-terminal amino acid (Ac-Leu-Lys-Lys-Thr-Glu-Thr-Gln-OH)
- White to off-white solid, soluble in water with a solubility of 50 mg in 1 mL water
- No USP drug substance monograph
- BDS Storage and Stability
  - Long-term storage condition: Store in a sealed container away from moisture and light under nitrogen atmosphere at temperatures -80°C for 2 years and -20°C for a year in powder form
  - In solvent, TB-500 (free base) should be stored in a sealed container away from moisture and light under nitrogen atmosphere at temperatures -80°C for 6 months and -20°C for one month
  - Sensitive to product formulation, process, and environmental conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (2)

- Potential impurities for peptide
  - Peptide-related impurities: due to incomplete coupling reactions, truncations, or side reactions; peptide-related aggregates
  - Peptide synthesis process-related impurities: impurities in the protected amino acid starting materials (e.g., isomeric impurities, free amino acids), residual solvents, coupling reagents, activators, catalysts, and scavengers
- No CoA for TB-500 (free base) in the nomination
- CoA found from public domain
  - No information on impurity limits/testing results
  - Lack of information on the potential for peptide aggregation
  - Lack of microbial bioburden and/or bacterial endotoxin tests
- Potential for immunogenicity
  - Associated with the impurities and peptide related aggregates, especially when formulated in an injectable dosage form

Physical and Chemical Characterization (3)

Conclusion

TB-500 (free base) is considered not well-characterized

- Inconsistent naming conventions that do not follow established chemical nomenclature standards
- Lack of certain critical characterization data, such as impurities, aggregates, microbial bioburden and/or bacterial endotoxin levels
- Potential for immunogenicity when formulated in an injectable dosage form due to potential for aggregation as well as peptide-related impurities

Physical and Chemical Characterization (4)

TB-500 Acetate

- Acetate salt form of TB-500 (free base), which is a seven amino acid synthetic fragment of thymosin β4 and an acetyl group at the N-terminal amino acid (Ac-Leu-Lys-Lys-Thr-Glu-Thr-Gln-OH)
- White to off-white powder, soluble in water - no solubility data available in the nomination and publicly available scientific literature
- No USP drug substance monograph
- BDS Storage and Stability
  - Long-term storage condition: Store in a sealed container at 2 °C to 8 °C - recommended in the CoA the nominator provided
  - Sensitive to product formulation, process, and environmental conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (5)

- Potential impurities for peptide
  - Peptide-related impurities: due to incomplete coupling reactions, truncations, or side reactions; peptide-related aggregates
  - Peptide synthesis process-related impurities: impurities in the protected amino acid starting materials (e.g., isomeric impurities, free amino acids), residual solvents, coupling reagents, activators, catalysts, and scavengers
- The CoA provided
  - No information regarding the nature of individual impurities. Such information also was not found from publicly available scientific literature.
  - Lack of information on the potential of peptide aggregation
  - Lack of microbial bioburden and/or bacterial endotoxin tests
- Potential for immunogenicity
  - Associated with the impurities and peptide related aggregates, especially when formulated in an injectable dosage form

Physical and Chemical Characterization (6)

Conclusion

TB-500 acetate is considered not well-characterized

- Inconsistent naming conventions that do not follow established chemical nomenclature standards
- Lack of certain critical characterization data, such as impurities, aggregates, microbial bioburden and/or bacterial endotoxin levels
- Potential for immunogenicity when formulated in an injectable dosage form due to potential for aggregation as well as peptide-related impurities

TB-500 (Free Base) or TB-500 Acetate

- The references reviewed do not clearly identify whether the substance discussed is TB-500 (free base) or TB-500 acetate
- In the next sections, the substances will be generally referred to as TB-500

General Pharmacology

- TB-500 is the N-acetylated heptapeptide N-acetyl-LKKTETQ (Ho et al. 2012; Sosne et al. 2010)
- TB-500 (N-acetyl-LKKTETQ) has the 6-amino acid sequence LKKTET that makes up the actin-binding region thought to contribute to the wound-healing properties of the full-length thymosin β4 peptide (Sosne et al. 2010)
- However, in an in-vitro study, TB-500 (50 µg/mL) did not promote “wound” closure when applied to cultured fibroblasts with uniform “wounds” generated by physical scratches (Rahaman et al. 2024)
- The nominator did not submit, and FDA did not identify, published nonclinical in-vivo studies assessing the potential effects of TB-500 on wounds

Pharmacokinetics

- In thoroughbred geldings treated with TB-500 (free base; 10 mg, SC), plasma concentrations of TB-500 peaked between 1- and 2-hour post-treatment and declined subsequently becoming unquantifiable between 6 and 10 hours (Ho et al. 2012)
- TB-500 (free base) delivered via the SC route of administration (ROA) to horses and the intraperitoneal ROA to rats reached the systemic circulation and was metabolically hydrolyzed into shorter peptides (Ho et al. 2012; Rahaman et al. 2024)
- At the time of this evaluation, the nominator did not submit, and FDA did not identify, published clinical studies assessing the pharmacokinetic profile of TB-500 delivered via any ROA in humans

Clinical Effectiveness

- The nominator listed the proposed use: “Wound healing”
  - The nominator has not provided information about what specific type of wound TB-500 is intended to be used for
  - Wounds can be serious or life-threatening
  - There are currently various FDA-approved therapies with established efficacy for the management of wounds
- The nominator did not provide clinical evidence on the use of TB-500 in wound healing
- FDA performed a search of published medical literature, and FDA did not find any information where TB-500 was administered to patients to treat any disease or condition

Conclusion: There is a lack of evidence to evaluate the effectiveness of TB-500 for wound healing

Nonclinical Safety

At the time of this evaluation, the nominator did not submit, and FDA did not identify, nonclinical toxicity studies to inform safety considerations for potential clinical uses of TB-500.

Clinical Safety (1)

- FDA Adverse Event Reporting System (FAERS):
  - Search retrieved no adverse event (AE) reports for TB-500[1]

- Human Food Program (HFP) Human Foods Complaint System (HFCS)
  - Search retrieved no reports that included safety assessments for TB-500

[1] Note the lack of reports for TB-500 does not imply that the substance is safe or lacks toxicities. FAERS data have limitations. Reporting is voluntary. FDA does not receive all AE reports that may potentially occur with a product, especially for compounded products.

Clinical Safety (2)

- The nomination did not include, and FDA has not identified, any clinical studies or human exposure data for TB-500 via any ROA
- Potential safety risks associated with the use of TB-500 in humans are unknown

Additional Safety Information – Immunogenicity Concerns

- TB-500 (free base) and TB-500 acetate reportedly contain 7 amino acids
- Peptides administered via injectable routes, such as the proposed for the IM and SC routes, may pose a significant risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities
- The nomination did not provide, and FDA did not identify, clinical studies or human exposure data assessing immunogenicity or aggregation of TB-500 -related BDSs

Safety - Conclusion

- There is lack of clinical and nonclinical safety information on the use of TB-500 (free base) and TB-500 acetate
- FDA is concerned about the lack of human data on drug products containing TB-500 administered via any ROA, including lack of information to assess immunogenic and aggregation safety risks
- Potential safety risks associated with the use in humans are unknown
- There are currently available FDA-approved therapies for the management of wounds

Historical Use in Compounding (1)

- The nominator stated that TB-500 has been used to compound drug products but did not provide any additional information regarding the historical use of TB-500 in compounding
- TB-500 appears to have first been synthesized in 2003
- No studies were found in the literature in which TB-500 was administered to humans
- Not recognized in the European or Japanese Pharmacopeias or in any of the National Medical Registries searched

Historical Use in Compounding (2)

- An analysis of online discussion forums to identify trends in popularity of doping products identified that TB-500 emerged as a topic of discussion after 2010 and the number of discussions regarding its use have continued to trend upward (Pineau et al. 2016)
  - TB-500 is on the World Anti-Doping Agency's prohibited list under the Growth Factors and Growth Factor Modulators section (S2.3)

Historical Use in Compounding (3)

- TB-500 appears to be offered online for use in a variety of conditions
  - Uses include, but are not limited to:
    - Promoting tissue repair and regeneration
    - Healing damage to tendons, muscles, and ligaments
    - Wound healing
    - Reducing inflammation
    - Improving flexibility and mobility
  - Some sites state that TB-500 is obtained from a compounding pharmacy
    - FDA was unable to identify any pharmacies that compound products containing TB-500
- No outsourcing facility has reported compounding drug products containing TB-500-related BDSs to FDA

Historical Use in Compounding (4)

Conclusion

The extent to which TB-500-related BDSs have been used in compounding is unclear. Currently available data and published literature are too limited for FDA to understand the historical use of TB-500-related BDSs in compounded drug products.

Evaluation Conclusion

- A balancing of the criteria weighs against TB-500 (free base) or TB-500 acetate being placed on the 503A Bulks List
- FDA's conclusion is based on the following facts:
  - These substances are not well-characterized from a physical and chemical characterization perspective
  - The extent of use in compounding is unknown
  - There is a lack of information on their use when administered in humans to make a conclusion on their clinical safety and effectiveness
- There are currently FDA-approved therapies for the management of wounds

Recommendation

FDA is proposing that TB-500 (free base) and TB-500 acetate NOT be included on the 503A Bulks List


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ADMINISTRATION

MOTS-c-Related Bulk Drug Substances: MOTS-c (Free Base) and MOTS-c Acetate

Pharmacy Compounding Advisory Committee Meeting

July 23, 2026

Center for Drug Evaluation and Research (CDER)
U.S. Food & Drug Administration (FDA)

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Introduction

- Mitochondrial Open Reading Frame of 12S rRNA-c (MOTS-c)-related bulk drug substances (BDSs) were nominated for inclusion on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (503A Bulks List)
  - MOTS-c (free base)
  - MOTS-c acetate

- There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for MOTS-c (free base) or its acetate form

- Neither is a component of an FDA-approved drug

Nomination

- MOTS-c-related BDSs were nominated for the following uses:
  - Insulin resistance
  - Obesity
  - Osteoporosis
  - Vascular calcification
  - Muscle/fat metabolism
  - Longevity

- Nominated products
  - Subcutaneous injection (SC)
  - 5 mg and 10 mg dosage strengths

- The nomination was withdrawn, and FDA is evaluating these substances at its discretion

Evaluation Criteria

- Physical and chemical characterization
- Available evidence of effectiveness or lack of effectiveness
- Safety Concerns
- Historical use in compounding

BDS Nomenclature

- MOTS-c is a common name and not a USAN, INN or IUPAC name
- FDA has encountered multiple salts and derivatives, including different active moieties, being marketed under the same common name
    - Inconsistent naming conventions can contribute to a potential safety risk for patients
- USAN program and other naming conventions exist to ensure that the patient is provided with the drug the prescriber intended

USAN: United States Adopted Name
INN: International Non-proprietary Name
IUPAC: International Union of Pure and Applied Chemistry

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

	MOTS-c (Free Base)	MOTS-c Acetate
UNII Code	A5CV6JFB78	Not available
CAS No.	1627580-64-6	CAS number of the free base is used
MF/MW (g/mol)	$C_{101}H_{152}N_{28}O_{22}S_2$/2174.6	$C_{101}H_{152}N_{28}O_{22}S_2 \cdot CH_3COOH$/2234.64
Peptide sequence	H-Met-Arg-Trp-Gln-Glu-Met-Gly-Tyr-Ile-Phe-Tyr-Pro-Arg-Lys-Leu-Arg-OH	H-Met-Arg-Trp-Gln-Glu-Met-Gly-Tyr-Ile-Phe-Tyr-Pro-Arg-Lys-Leu-Arg-OH $\cdot CH_3COOH$
Supplier	Yes	Yes
Active moiety	MOTS-c (free base)	MOTS-c (free base)

UNII: Unique Ingredient Identifier; CAS: Chemical Abstracts Service; MF: molecular formula; MW: molecular weight

Summary of Information Submitted in the Withdrawn Nomination

Nominator	Nomination 1
Nominated BDS	MOTS-c
BDS per UNII code	A5CV6JFB78 (*matches MOTS-c free base*)
CoA	CoA provided for MOTS-c Acetate
CAS No.	1627580-64-6 (*matches MOTS-c free base*)
MF	$C_{101}H_{152}N_{28}O_{22}S_2$ (*provided in the nomination package that matches MOTS-c free base*)
MW	Not provided
Chemical Name	(4S)-4-[[(2S)-5-amino-2-[[(2S)-2-[[(2S)-2-[[(2S)-2-amino-4-methylsulfanylbutanoyl]amino]-5-carbamimidamidopentanoyl]amino]-3-(1H-indol-3-yl)propanoyl]amino]-5-oxopentanoyl]amino]-5-[[(2S)-1-[[2-[[(2S)-1-[[(2S,3S)-1-[[(2S)-1-[[(2S)-1-[(2S)-2-[[(2S)-1-[[(2S)-6-amino-1-[[(2S)-1-[[(1S)-4-carbamimidamido-1-carboxybutyl]amino]-4-methyl-1-oxopentan-2-yl]amino]-1-oxohexan-2-yl]amino]-5-carbamimidamido-1-oxopentan-2-yl]carbamoyl]pyrrolidin-1-yl]-3-(4-hydroxyphenyl)-1-oxopropan-2-yl]amino]-1-oxo-3-phenylpropan-2-yl]amino]-3-methyl-1-oxopentan-2-yl]amino]-3-(4-hydroxyphenyl)-1-oxopropan-2-yl]amino]-2-oxoethyl]amino]-4-methylsulfanyl-1-oxobutan-2-yl]amino]-5-oxopentanoic acid (*matches MOTS-c free base*)
Proposed Products	5 mg and 10 mg for subcutaneous (SC) injection

Italics in the table above represents the information identified by the FDA.
CoA: Certificate of Analysis

Critical Quality Attributes (CQAs) for Nominated Dosage Form

SC Injection:

- Bioburden load (i.e., microbial enumeration test)
- Bacterial Endotoxins Test (BET)
- Solubility

Physical and Chemical Characterization (1)

MOTS-c (Free Base):

- A 16-amino-acid peptide encoded by a short open reading frame (sORF) within the mitochondrial 12S rRNA (mitochondrial open-reading-frame of the twelve S rRNA type-c)
- White to off-white lyophilized powder, lack of information on the water solubility data in either nomination or publicly scientific literature
- No USP drug substance monograph
- BDS Storage and Stability:
  - Long-term storage condition: Stored at -20°C desiccated and protected from light in a tightly closed container.
  - Upon reconstitution, keep/store the solution at 4°C between 2 -7 days, and for future use, below -18°C.
  - Sensitive to product formulation, manufacturing processes, and environmental conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (2)

- Potential impurities for peptide:
  - Peptide-related impurities: due to incomplete coupling reactions, truncations, or side reactions; peptide-related aggregates
  - Peptide synthesis process-related impurities: impurities in the protected amino acid starting materials (e.g., isomeric impurities, free amino acids), residual solvents, coupling reagents, activators, catalysts, and scavengers
- No CoA for MOTS-c (free base) in the nomination
- CoAs found from public domain:
  - No information on impurity limits/testing results
  - Lack of information on the potential of peptide aggregation
  - Lack of microbial bioburden and/or bacterial endotoxin tests
- Potential for immunogenicity
  - Associated with the impurities and peptide related aggregates, especially when formulated in an injectable dosage form

Physical and Chemical Characterization (3)

Conclusion: MOTS-c (free base) is considered not well-characterized:

- Inconsistent naming conventions that do not follow established chemical nomenclature standards
- Lack of certain critical characterization data, such as impurities, aggregates, microbial bioburden and/or bacterial endotoxin levels
- Potential for immunogenicity when formulated in an injectable dosage form due to potential for aggregation as well as peptide-related impurities
- Lack of water solubility data as well as the reconstituted concentration of proposed injectable final product, it is difficult to draw a conclusion if the water solubility will be a potential issue to impact product performance for the proposed injectable dosage form.

Physical and Chemical Characterization (4)

MOTS-c Acetate:

- Acetate salt form of MOTS-c (free base)
- White to off-white powder, soluble in water at 6.25 mg/mL
- No USP drug substance monograph
- BDS Storage and Stability:
  - Long-term storage condition: stable at -80°C for 2 years or at -20°C for 1 year
  - Upon reconstitution, stable at -80°C for 6 months or at -20°C for 1 month
  - Sensitive to product formulation, manufacturing processes, and environmental conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (5)

- Potential impurities for peptide:
  - Peptide-related impurities: due to incomplete coupling reactions, truncations, or side reactions; peptide-related aggregates
  - Peptide synthesis process-related impurities: impurities in the protected amino acid starting materials (e.g., isomeric impurities, free amino acids), residual solvents, coupling reagents, activators, catalysts, and scavengers
- The CoA provided:
  - No information on the impurity limits/testing results.
  - Lack of information on the potential of peptide aggregation
  - Lack of microbial bioburden and/or bacterial endotoxin tests
  - All these information could also not be found in publicly available scientific literature
- Potential for immunogenicity
  - Associated with the impurities and peptide related aggregates, especially when formulated in an injectable dosage form

Physical and Chemical Characterization (6)

Conclusion: MOTS-c acetate is considered not well-characterized:

- Inconsistent naming conventions that do not follow established chemical nomenclature standards
- Lack of certain critical characterization data, such as impurities, aggregates, microbial bioburden and/or bacterial endotoxin levels
- Potential for immunogenicity when formulated in an injectable dosage form due to potential for aggregation as well as peptide-related impurities
- Difficult to evaluate how the water solubility of MOTS-c acetate will impact the performance of the proposed injectable final product due to lack of information on how to compound the proposed injectable product with known concentration

MOTS-c (free base) or MOTS-c Acetate

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

General Pharmacology (1)

- Pharmacological effects of MOTS-c identified in published nonclinical studies include:
  - Suppression of diet-induced obesity and diet- and age-dependent insulin resistance in mice (Kim et al. 2019; Lee et al. 2015; Lee et al. 2016)
  - Promotion of osteogenesis in rat bone mesenchymal stem cells in vitro (Hu and Chen 2018)
  - Inhibition of osteolysis in vivo and in vitro (Yan et al. 2019)
  - Reduction of vascular calcification and associated myocardial remodeling in a rat model of vascular calcification (Wei et al. 2020)

General Pharmacology (2)

- Proposed mechanism of action
  - Researchers have proposed that MOTS-c, via stimulation of adenosine monophosphate-activated protein kinase (AMPK) signaling, can regulate nuclear expression of genes involved in metabolic homeostasis (Lee et al. 2016). The mechanism(s) by which MOTS-c stimulates AMPK signaling are poorly understood.

- Limitations of the published nonclinical pharmacological studies of MOTS-c
  - Studies limited to in-vitro models and small rodent models
  - Lack of assessments of dose-response relationships for the effects of MOTS-c in vivo
  - The molecular targets through which MOTS-c acts are unknown, making it difficult to predict which organs might be targeted and affected by MOTS-c

Clinical Effectiveness

- MOTS-c-related BDSs were nominated for the following uses:
  - Insulin resistance
  - Obesity
  - Osteoporosis
  - Vascular calcification
  - Muscle/fat metabolism
  - Longevity
- The nominator did not provide clinical evidence on the use of MOTS-c-related BDSs for the proposed uses
- FDA did not identify data, such as publicly available clinical studies, evaluating the administration of MOTS-c-related BDS to humans
- **Conclusion:** There is a lack of evidence to evaluate the effectiveness of the MOTS-c-related BDSs for the nominated uses

Nonclinical Safety

- The nominator did not submit, and FDA did not identify, published in-vivo nonclinical pharmacokinetic studies of MOTS-c-related BDSs
  - In-vitro incubation of MOTS-c (5 µg/mL, 37°C, 15-60 minutes) with human whole blood results in rapid proteolytic hydrolysis of MOTS-c into shorter peptides
  - It is unclear whether exogenous administration of MOTS-c to humans via the nominated SC route can generate pharmacologically active concentrations of the peptide over time

- The nominator did not submit, and FDA did not identify, published nonclinical toxicity studies to inform safety considerations for potential clinical uses of MOTS-c (free base) or MOTS-c acetate

Clinical Safety
PK, FAERS

- Pharmacokinetics (PK)
  - The nominator did not submit, and FDA did not identify, publicly available clinical studies that provided pharmacokinetic (PK) data for MOTS-c-related BDSs

- FDA Adverse Event Reporting System (FAERS)[1]
  - No Adverse Event (AE) reports

1. Note the lack of reports for MOTS-c does not imply that the substance is safe or lacks toxicities. FAERS data have limitations. Reporting is voluntary. FDA does not receive all AE reports that may potentially occur with a product, especially for compounded products.

Clinical Safety - Clinical Studies

- The nomination did not include, and FDA has not identified, any publicly available clinical studies or human exposure data for MOTS-c-related BDSs via any route of administration (ROA)

Immunogenicity

- MOTS-c-related BDSs are reported to contain 16 amino acids
- FDA is concerned about potential for immunogenicity when administered by an injection ROA as proposed, due to the potential for aggregation, as well as potential peptide-related impurities
- The nominator did not provide, and FDA did not identify, clinical studies assessing immunogenicity or aggregation of MOTS-c-related BDSs

Clinical Safety Conclusions

- There is a lack of clinical and nonclinical safety information on the use of MOTS-c-related BDSs
- There is a lack of human data on drug products containing MOTS-c-related BDSs administered via any route of administration
- MOTS-c is a peptide reported as containing 16 amino acids for which there is a lack of information to assess its immunogenic safety risk

Historical Use in Compounding (1)

- The earliest use and extent of MOTS-c use in compounding is unknown
- No studies were found in the literature in which a compounded drug product containing a MOTS-c-related BDS was administered
- Compounded drug products containing MOTS-c appear to be offered online in the United States:
  - As single and multiple peptide injectable products
  - For uses such as regulating mitochondrial energy, promoting the metabolism of fatty acid in the liver; promoting metabolic homeostasis; improving glucose regulation; aiding in the resistance of metabolic stress; protecting against insulin resistance; promoting weight loss, and improving physical performance

Historical Use in Compounding (2)

- MOTS-c is a prohibited substance on The Global Drug Reference Online database
- MOTS-c (free base) and MOTS-c acetate are not recognized in the European Medicines Agency website or European or Japanese Pharmacopoeias

Historical Use in Compounding (3)

Conclusion

The extent to which MOTS-c-related BDSs have been used in compounding is unknown. Published literature did not reveal studies in which compounded drug products containing MOTS-c-related BDSs were used in humans. Internet search results indicate that websites appear to offer compounded drug products containing MOTS-c-related BDSs in various formulations for a variety of uses.

Evaluation Conclusion

- A balancing of the criteria weigh against MOTS-c (free base) and MOTS-c acetate being placed on the 503A Bulks List.
- FDA's conclusion is based on:
  - These substances are not well characterized from a physical and chemical perspective
  - Lack of evidence to support the effectiveness of the MOTS-c-related BDSs for the nominated uses
  - No information on the use of MOTS-c-related BDSs administered in humans
  - Lack of clinical and nonclinical safety information on the use of MOTS-c-related BDSs
  - Lack of human data on drug products containing this substance administered via any route of administration
  - MOTS-c is reported to be a peptide containing 16 amino acids for which there is a lack of information to assess its immunogenic safety risk
  - Extent of use of MOTS-c-related BDS in compounding is unknown

Recommendation

FDA is proposing that MOTS-c (free base) and MOTS-c acetate NOT be included on the 503A Bulks List.


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