FDA Briefing Document

Pharmacy Compounding Advisory Committee (PCAC) Meeting

December 4, 2024

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.

AOD-9604-Related Bulk Drug Substances (AOD-9604 (free base) and AOD-9604 Acetate)

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FDA Evaluation of AOD-9604-Related Bulk Drug Substances (AOD-9604 (free base) and AOD-9604 acetate)

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TO: Pharmacy Compounding Advisory Committee

U.S. Food & Drug Administration
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SUBJECT: Evaluation of AOD-9604-related Bulk Drug Substances (AOD-9604 (free base) and AOD-9604 acetate) for Inclusion on the 503A Bulk Drug Substances List

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I. INTRODUCTION

FDA received nominations for AOD-9604 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] The nominators of AOD-9604-related BDSs provided inconsistent information in the nomination package regarding the specific BDS proposed. Specifically, it is unclear whether one of the nominations was for AOD-9604 (free base) or AOD-9604 acetate. AOD-9604 (free base) and AOD-9604 acetate are different BDSs. Please see additional information in section II.A. The nominations were withdrawn[2] and FDA is evaluating the substances at its discretion.

AOD-9604 is a hexadecapeptide that is a synthetic fragment of human growth hormone (hGH) (15 amino acids: 177-191) with an additional tyrosine at the N-terminal end. Peptides such as AOD-9604 have specific considerations that differentiate them from small molecule drugs due to their composition which may include immunogenic potential, peptide self-association and aggregation, the potential for peptide-related impurities, and challenges in characterization. Although it is unclear whether the nominators intended to nominate AOD-9604 (free base) or AOD-9604 acetate, due to FDA's significant safety concerns related to the use of certain peptides in compounded drug products, FDA has decided to evaluate both on its own initiative.

We evaluated AOD-9604 (free base) and AOD-9604 acetate for the treatment of obesity.[3,4,5] The AOD-9604-related drug products proposed in the nominations were: 1,200 mcg/mL for subcutaneous (SC) injection, 600 mcg oral capsule, and 600 mcg/gm topical cream for transdermal route of administration.

There is no applicable United States Pharmacopeia (USP) or National Formulary (NF) drug substance monograph for AOD-9604 (free base) or its acetate form, and neither is a component of an FDA-approved drug.

We have evaluated publicly available data on the physicochemical characteristics, historical use, effectiveness, and safety in compounding of these substances. For the reasons discussed below, we believe the evaluation criteria ***weigh against*** placing AOD-9604 (free base) or AOD-9604

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[1] Nominations that had been submitted include: Nomination from Wells Pharmacy for AOD-9604 (Document ID: FDA-2015-N-3534-0283) can be accessed at: https://www.regulations.gov/document/FDA-2015-N-3534-0283, Wells Pharmacy's subsequent docket comment submission (Docket ID: FDA-2015-N-3534-0467) can be accessed at: https://www.regulations.gov/document/FDA-2015-N-3534-0467 with additional information that was evaluated in this memo; Nomination from International Peptide Society (LDT) for AOD-9604 (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 AOD-9604 (free base) and AOD-9604 acetate on its own initiative, FDA considered information submitted in these nominations as part of this evaluation.

[2] Document IDs: FDA-2015-N-3534-0471 and FDA-2015-N-3534-0472.

[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] AOD-9604 was nominated for the following uses: weight loss, osteoporosis and osteoarthritis. For reasons detailed in Section II.C., FDA did not evaluate whether AOD-9604 is appropriate for use in osteoporosis and osteoarthritis.

[5] AOD-9604 was nominated for the use "weight loss." For reasons detailed in Section II.C.1., FDA evaluated it for the use listed above, obesity.

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?[6]

As discussed above, this evaluation pertains to AOD-9604 (free base) and AOD-9604 (acetate).

A BDS or active pharmaceutical ingredient (API)[7] used in a drug product may be a free base or a salt or an ester of the free base, all of which share the same active moiety.[8] 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:

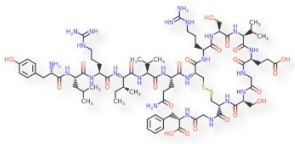
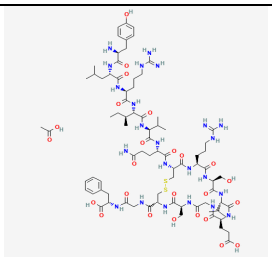
Table 1. Summary of Basic Information on AOD-9604 (Free base) and AOD-9604 Acetate.

	AOD-9604 (Free base)	**AOD-9604 Acetate**
UNII Code	7UP768IP4M	Not available
***CAS No.**	221231-10-3	Not available

[6] 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).

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

[8] "*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 AOD-9604 (Free base) and AOD-9604 Acetate.		
	AOD-9604 (Free base)	**AOD-9604 Acetate**
Molecular Weight (g/mol)/ Molecular Formula	1,815.09/ $C_{78}H_{123}N_{23}O_{23}S_2$	1,875.1/ $C_{80}H_{127}N_{23}O_{25}S_2$
****Chemical Structure**		
Supplier[9]	Yes	Yes
Active Moiety	AOD-9604 (free base)	AOD-9604 (free base)

*Discrepancies have been found in the CAS No. reported for AOD-9604 in public domain. (Some suppliers have reported CAS No. 386264-39-7 for AOD-9604.);[10] **Inconsistencies are also noted between the chemical structure and the amino acid sequence provided for AOD-9604 by some suppliers at their websites.[11]

Two nominations were submitted, which, as discussed above, were later withdrawn. One of the nominations submitted provided inconsistent information in its nomination package, which include (1) nominated BDS is AOD-9604 (free base) but the BDS in the accompanying Certificate of Analysis (CoA) is AOD-9604 acetate, and (2) the CAS number, molecular formula and molecular weight provided in the CoA of AOD-9604 acetate is for the free base. All chemistry-related information about the BDSs provided by the two nominators is summarized in Table 2.

[9] 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.
[10] Supporting links for the statement: https://www.alfa-chemistry.com/cas_386264-39-7.htm. Accessed 9/19/24.
[11] Supporting links for the statement: https://pubchem.ncbi.nlm.nih.gov/compound/71300630, https://pubchem.ncbi.nlm.nih.gov/substance/319360420#section=External-ID, https://origincompounds.com/shop/all-p roducts/aod-9604/. Accessed 9/12/24.

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

Nominator	1	2
Nominated BDS	AOD-9604 (free base)	AOD-9604 (free base)
BDS per UNII code	Not provided	7UP768IP4M *(matches AOD-9604 free base)*
CoA	CoA provided for AOD-9604 (free base)	CoA provided for AOD-9604 Acetate
CAS No.	221231-10-3 *(matches AOD-9604 free base)*	221231-10-3 *(matches AOD-9604 free base)*
Molecular Formula	$C_{78}H_{123}N_{23}O_{23}S_2$ *(provided in the CoA) (matches AOD-9604 free base)*	$C_{78}H_{123}N_{23}O_{23}S_2$ *(provided in the nomination package and CoA) (matches AOD-9604 free base)*
Molecular Weight	1,815.1 *(provided in the CoA) (matches AOD-9604 free base)*	1,815.1 *(provided in the CoA) (matches AOD-9604 free base)*
Chemical Name	L-tyrosyl-L-leucyl-L-arginyl-L-isoleucyl-L-valyl-L-glutaminyl-L-cysteinyl-L-arginyl-L-seryl-L-valyl-L-alpha-glutamyl-glycyl-L-seryl-L-cysteinyl-glycyl-L-phenylalanine (7->14)-disulfide *(matches AOD-9604 free base)*	L-tyrosyl-L-leucyl-L-arginyl-L-isoleucyl-L-valyl-L-glutaminyl-L-cysteinyl-Larginyl-L-seryl-L-valyl-L-alpha-glutamyl-glycyl-L-seryl-L-cysteinyl-glycyl-Lphenylalanine (7->14)-disulfide *(matches AOD-9604 free base)*
Active Moiety in Clinical References	AOD-9604 (free base)	AOD-9604 (free base)

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

FDA is choosing to concurrently evaluate both BDSs, AOD-9604 (free base) and AOD-9604 acetate, in this section under two different sub-sections (II.A.1 and II.A.2) and will provide a separate conclusion for each BDS.

The nominators proposed to compound the BDSs into the following dosage forms:

- Subcutaneous injectable
- Transdermal cream
- Oral capsule

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

For a product in a transdermal cream dosage form, polymorphism of the API, particle size, microbial limit, and viscosity are critical attributes to ensure the efficacy of the drug product.

For a product in an oral capsule dosage form, polymorphism of the API, dissolution, microbial limit, particle size distribution and oral bioavailability of the API are critical attributes for the quality control.

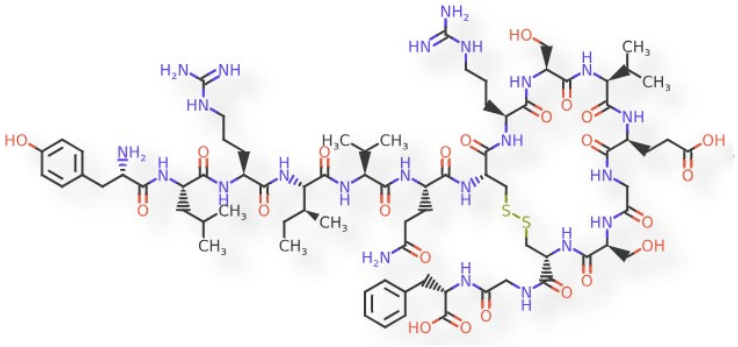
There is no USP drug substance monograph for AOD-9604 (free base) or its acetate salt form. We reviewed physical and chemical characterization-related information provided by the nominators and performed a literature search for additional information on AOD-9604 (free base) and its acetate salt. Databases such as SciFinder, Analytical Profiles of Drug Substances, PubMed, the European Pharmacopoeia, and the USP-NF were searched for information on AOD-9604 (free base) and AOD-9604 acetate.

1. AOD-9604 (Free base)

AOD-9604 (free base) is a hexadecapeptide, i.e., it contains 16 amino acids. It is a synthetic 177-191 fragment (15 amino acids) of hGH with an additional tyrosine at the N-terminal end. In addition, two cysteine amino acids are cyclized to form a disulfide linker, as shown in Figure 1 below. The molecular formula of AOD-9604 (free base) is $C_{78}H_{123}N_{23}O_{23}S_2$, and its molecular weight is 1,815.09 g/mol.

A CoA of AOD-9604 (free base) from Attix Pharmaceuticals, which was included in one of the nominations, provided the testing attribute results, including appearance, solubility in water, identification, peptide purity, water content and assay. Testing results are not provided for the control on impurities, aggregates, and microbial limits/bacterial endotoxin levels.

Figure 1. Chemical Structure of AOD-9604 (free base).[12]



a. Stability of the active pharmaceutical ingredient (API) and likely dosage forms

As reported in the safety data sheet by Particle Peptides,[13] AOD-9604 (free base) is stored in a dry place to protect against water and moisture. It should be stored in closed containers at temperatures of -18 °C for 3 years, 0-7 °C for 1 year, and 7-30 °C for half a year. As per the

[12] https://gsrs.ncats.nih.gov/ginas/app/beta/substances/7UP768IP4M . Accessed 5/24/24.
[13] https://particlepeptides.com/img/cms/SDS_AOD-9604.pdf . Accessed 5/27/24.

Attix Pharmaceuticals CoA, long-term storage conditions for AOD-9604 (free base) is in tight vials in freezer.

FDA notes that peptides such as AOD-9604 (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 AOD-9604 (free base), 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. 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 bulk drug substance synthesis

AOD-9604 (free base) is a synthetic peptide developed by Metabolic Pharmaceuticals Limited, which is synthesized with solid-phase synthesis procedure and purified using reverse-phase high-performance liquid chromatography (HPLC) methodology (Heffernan, 2001).

Another synthesis of AOD-9604 (free base) was reported in *International Journal of Peptide Research and Therapeutics* (van Lierop 2010), which utilized the manual and microwave-accelerated Solid Phase Peptide Synthesis (SPPS) technique to prepare the linear peptide precursor for final cyclization. After the cleavage of resin and sidechain protecting group, the linear peptide on 2,2'-dipyridyl disulfide catalyzed oxidation in presence of 6M guanidine hydrochloride in water (1:9) afforded AOD-9604 (free base) with >95% purity after preparative reverse phase HPLC.

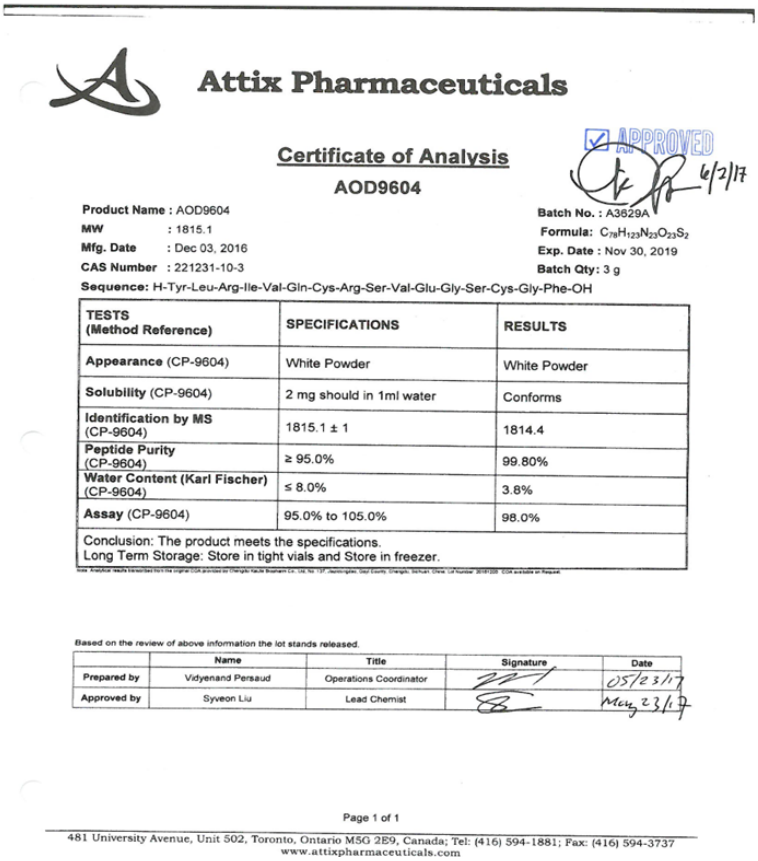
In an alternative approach published in *Organic Letters*, Spengler and collaborators reported the synthesis of AOD-9604 (free base) by employing Native Chemical Ligation (NCL) method with N-methylbenzimidazolinone (MeNbz) as linker for preparing linear peptide precursor. This linear peptide on oxidative cyclization provided AOD-9604 (free base) (Spengler et al. 2018).

c. Likely impurities[14]

[14] 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. If likely impurities of concern (e.g., nitrosamines, potential mutagenic substances, and potential teratogenic substances) are identified in the CoAs or the literature of the nominated bulk drug substance, available nonclinical toxicity data for those impurities are discussed in the Nonclinical Assessment at Section II.D.1 as part of the safety assessment of the substance.

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 AOD-9604 (free base). For most synthetic peptides, the solid-phase peptide synthesis method has been widely used by industry for peptide synthesis. The solid phase synthesis of peptides may lead to potential peptide-related impurities due to incomplete coupling reactions, truncations, or side reactions. These peptide-related impurities are typically similar in structure to the target peptide and may be difficult to identify and quantify without sophisticated analytical methods. Additional potential common impurities may include starting materials which typically include protected amino acids, 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 limited or no information on the impurity limits/testing results as attribute control in the Attix Pharmaceuticals CoA (see below) and in the other CoAs that FDA identified from a detailed literature search [15]



Attix Pharmaceuticals

APPROVED 6/2/17

Certificate of Analysis

AOD9604

Product Name : AOD9604
MW : 1815.1
Mfg. Date : Dec 03, 2016
CAS Number : 221231-10-3
Sequence: H-Tyr-Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe-OH

Batch No. : A3629A
Formula: $C_{78}H_{123}N_{23}O_{23}S_2$
Exp. Date : Nov 30, 2019
Batch Qty : 3 g

TESTS (Method Reference)	SPECIFICATIONS	RESULTS
Appearance (CP-9604)	White Powder	White Powder
Solubility (CP-9604)	2 mg should in 1ml water	Conforms
Identification by MS (CP-9604)	1815.1 ± 1	1814.4
Peptide Purity (CP-9604)	≥ 95.0%	99.80%
Water Content (Karl Fischer) (CP-9604)	≤ 8.0%	3.8%
Assay (CP-9604)	95.0% to 105.0%	98.0%
Conclusion: The product meets the specifications. Long Term Storage: Store in tight vials and Store in freezer.		

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

	Name	Title	Signature	Date
Prepared by	Vidyanand Persaud	Operations Coordinator		05/23/17
Approved by	Syveon Liu	Lead Chemist		May 23/17

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www.attixpharmaceuticals.com

Based on the literature search conducted to understand the AOD-9604 (free base) impurity profile, the most common impurities for AOD-9604 (free base) are caused by the reduction of

[15] https://aminousa.com/products/aod-9604-10mg; https://skyepeptides.com/skyepeptides/wp-content/uploads/2024/02/coa-aod9604-02022024.pdf; https://transformapeptides.com/wp-content/uploads/2024/08/COA_AOD-9604_5mg_2024-08-13.pdf. Accessed 10/21/2024.

the disulfide bond, dimer formation and aggregate formation via disulfide bridges (Janvier et al. 2018a; Janvier et al. 2018b). However, this information is very limited.

Since there is lack of information regarding potential impurities (individual or amount) that can be present in AOD-9604 (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 as different impurities, or different amounts of the same impurity can be associated with potential immunogenicity.

d. Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism

AOD-9604 (free base) is reported as a white solid powder,[16] which is soluble in water up to 2 mg of AOD-9604 (free base) in 1 mL water as described in the submitted CoA (from Attix Pharmaceuticals). For SC injectable dosage form, polymorphism (exists in several crystalline forms) of the BDS is not critical to the performance of the final drug product as it is in liquid form prior to the administration. However, polymorphism of the BDS is a critical attribute for dosage forms including transdermal cream and oral capsule. Nominations and literature search did not provide any information on the particle size and polymorphism of AOD-9604 (free base).

e. Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize

The Attix Pharmaceuticals CoA of AOD-9604 (free base) does not control microbial limits/bacterial endotoxin levels in addition to impurities/aggregates. No additional relevant information regarding the physical and chemical characterization of AOD-9604 (free base) was identified from public domain.

Conclusions: AOD-9604 (free base) is a peptide containing 16 amino acids with a disulfide bond between two cysteines at position 7 and 14. The presence of this disulfide bridge can lead to degradation by reducing the disulfide bond and aggregate formation (Janvier et al. 2018a; Janvier et al. 2018b).

AOD-9604 (free base) is considered to be not physically and chemically well characterized because certain critical characterization data specific to AOD-964 (free base), such as potential peptide impurities, were not found in publicly available scientific literature and the provided CoA. Specific tests for AOD-9604 (free base) are not available in the public domain as well as in the submitted CoA, such as tests for impurities, aggregates, microbial test, and bacterial endotoxin test. As discussed in Section II.D.2.d, FDA is concerned about the potential for immunogenicity of AOD-9604 (free base) when formulated in an injectable dosage form for SC administration due to the potential for aggregation as well as potential peptide-related impurities, as discussed in the impurities section. Injectable routes of administration may present a particular risk for immunogenicity. We also note that the stability, pharmacological activity, and

[16] https://particlepeptides.com/img/cms/SDS_AOD-9604.pdf. Accessed 5/27/24.

immunogenic properties of peptides such as AOD-9604 (free base) are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

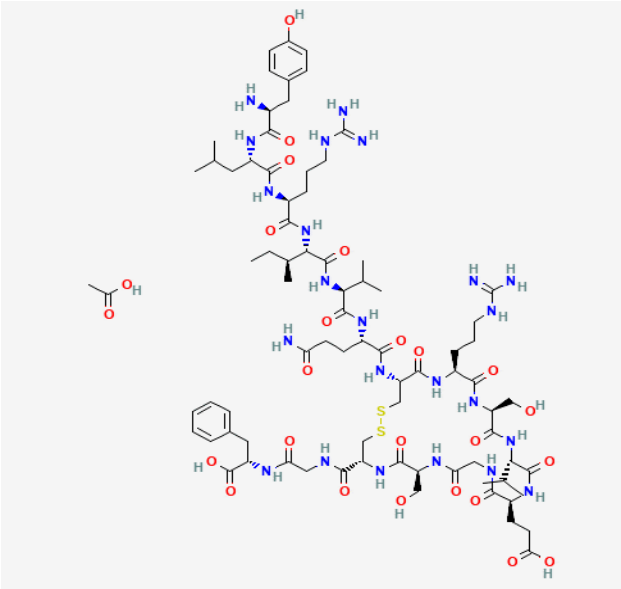
In addition, the nominators proposed transdermal cream and/or oral capsule as anticipated pharmaceutical dosage forms, in which polymorphism of the BDS is a critical attribute to ensure the efficacy of the compounded/finished drug product. However, information regarding the polymorphism of AOD-9604 (free base) is not available in the nomination packages as well as from the literature search.

2. AOD-9604 Acetate

AOD-9604 acetate is the acetate salt form of AOD-9604 (Figure 2). AOD-9604 acetate is reported as a white to off-white powder and the molecular formula and molecular weight are $C_{80}H_{127}N_{23}O_{25}S_2$ and 1,875.1 g/mol, respectively.

One of the withdrawn nominations provided two CoAs for AOD-9604 acetate with the nomination, one from Darmerica in the original nomination package and another from Biopeptek in their response to the previously noted information request. The CoA from Darmerica included the test results of appearance, solubility, identification, water content (Kalf Fischer, KF), peptide purity (HPLC), acetate content and assay (anhydrous, acetic acid free). Testing results were not provided for the control on impurities, aggregates, and microbial limits/bacterial endotoxin levels. Biopeptek's CoA includes the testing attribute results of identification, assay purity, related substances (% total impurities: ≤2.0%, % largest single impurity: ≤1.0%), peptide content, water content (KF), residual solvents, and bacterial endotoxins. Again, testing results were not provided for the control on aggregates, and microbial limits.

Figure 2. Chemical Structure of AOD-9604 Acetate. [17]



[17] https://pubchem.ncbi.nlm.nih.gov/compound/156599045. Accessed 5/24/24.

a. Stability of the API and likely dosage forms

The recommended storage temperature for AOD-9604 acetate is -20 °C. AOD-9604 acetate is reported to be stable for more than four years under this storage condition.[18] Based on the CoAs provided in one of the submitted nominations, AOD-9604 acetate should be stored in a sealed container at 2-8 °C in a fridge. For less than 6-month storage, the recommended condition is 2-8 °C and for more than 6-month storage, the recommended condition is -20 °C.

FDA notes that peptides such as AOD-9604 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 AOD-9604 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. 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 bulk drug substance synthesis

Synthesis of AOD-9604 acetate is not reported in the literature. Synthetic methods described in Section A1.2 for AOD-9604 (free base) is applicable for AOD-9604 acetate. A general method for the synthesis of acetate salt can be utilized for the synthesis of AOD-9604 acetate (Isidro-Llobet et al. 2019).

c. Likely impurities[19]

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 AOD-9604 acetate. For most synthetic peptides, solid-phase peptide synthesis method has been widely used by industry for peptide synthesis. The solid phase synthesis of peptides may lead to potential peptide-related impurities due to incomplete coupling reactions, truncations, or side reactions. These peptide-related impurities are typically similar in structure to the target peptide and may be difficult to identify and quantify without sophisticated analytical methods. Additional potential common impurities may include starting materials, typically protected amino acids, isomeric impurities, free amino acids, and other species that may carry over into the

[18] https://cdn.caymanchem.com/cdn/insert/36790.pdf. Accessed 5/27/24.

[19] 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. If likely impurities of concern (e.g., nitrosamines, potential mutagenic substances, and potential teratogenic substances) are identified in the CoAs or the literature of the nominated bulk drug substance, available nonclinical toxicity data for those impurities are discussed in the Nonclinical Assessment at Section D.I. as part of the safety assessment of the substance.

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.

The CoA from Biopeptek for AOD-9604 acetate, includes controls for the largest single impurity at a specification limit of ≤1.0% and total impurities at ≤2.0%. The CoA from Darmerica does not control for impurities. The CoA from Biopeptek is shown below.

biopeptek

CERTIFICATE OF ANALYSIS

Reference document : BPT-QC-STP-2001 V02

Product Name		AOD 9604 Acetate		
CAS No.		221231-10-3		
Molecular Formula		$C_{78}H_{123}N_{23}O_{23}S_2$		
Lot No.		GIM120230510		
Sequence		{Tyr}{Leu}{Arg}{Ile}{Val}{Gln}{Cys}{Arg}{Ser}{Val}{Glu}{Gly}{Ser}{Cys}{Gly}{Phe}		
Modifications		Disulfide bridge:7-14		
Storage Conditions		For less than 6-month storage, the recommended condition is 2-8℃; For longer term (> 6-month) storage, the recommended condition is minus 20℃.		
Test Items		**Specifications**	**Results**	**Method**
Appearance		White to off-white powder	White to off-white powder (Conforms)	BPT-QC-SOP-2001 V02
Identification	**Molecular Weight (MS)**	1815.1±1.0Da	1814.9Da	BPT-QC-SOP-2001 V02
	Retention Time (HPLC)	The retention time of the major peak of the sample solution corresponds to that of the standard solution	Conforms	BPT-QC-SOP-2001 V02
Assay	**Purity (HPLC)**	≥98.0%	98.8%	BPT-QC-SOP-2001 V02
	Related Substances (HPLC)	Total Impurities(%)≤2.0% Largest Single Impurity(%)≤1.0%	1.2% 0.4%	BPT-QC-SOP-2001 V02
	Peptide Content (HPLC)	≥80.0%	86.0%	BPT-QC-SOP-2001 V02
Specific Tests	**Water Content (Karl Fischer)**	≤8.0%	7.6%	BPT-QC-SOP-2001 V02; USP<921>
	Residual Solvent (GC; HPLC)	Acetonitrile≤0.041% Trifluoroacetic≤0.500%	0.001% N.D	BPT-QC-SOP-2001 V02
	Bacterial Endotoxins (Gel-clot Method)	<10EU/mg	Conforms	BPT-QC-SOP-2001 V02; USP<85>
Conclusion	This batch was tested following the *analytical procedure of BPT-QC-SOP-2001 V02;* The test results met the *specifications of BPT-QC-STP-2001 V02* .			

Date of Mfg	10 May 2023	Date of Exp	09 May 2025
Date of Test	12 Jun 2023	Date of Release	12 Jun 2023
Quality Control: Yang Xu Yang Xu 12 Jun 2023 Reviewed		Quality Assurance: Yongna Zhao Yongna Zhao 12 Jun 2023 Approved	

Biopeptek Pharmaceuticals,LLC.

Corporate headquarters: 5 Great Valley Parkway. Suite 100 Malvern, PA 19355, U.S.A Tel: 610.643.4881 www.biopeptek.com

Manufactured and Packaged at the FDA registered facility: 218 Shuangyuan Road, Chengyang, Qingdao, Shandong 266000, China (CHN)

The peptide is chemically synthesized

Based on the literature search conducted to understand the AOD-9604 impurity profile, the most common impurities for AOD-9604 are caused by the reduction of the disulfide bond, dimer formation, and aggregate formation via disulfide bridges (Janvier et al. 2018a; Janvier et al. 2018b). However, this information is very limited. Because of the lack of information regarding the nature of individual impurities that can be present at up to 1.0% level and lack of information on the potential of peptide aggregation, there is a concern about the potential immunogenicity associated with these impurities and peptide related aggregates.

d. Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism

AOD-9604 acetate is reported as a white powder,[20] which is soluble in water at 2 mg of AOD-9604 acetate in 1 mL water as described in the submitted CoA from Darmerica. For the SC injectable dosage form, polymorphism of the BDS is not critical to the performance of the final drug product as it is in liquid form prior to the administration. However, polymorphism of the BDS is a critical attribute for dosage forms including transdermal cream and oral capsule. Literature search did not provide any information on the particle size and polymorphism of AOD-9604 acetate.

e. Any other information about the substance that may be relevant, such as whether the API is poorly characterized or difficult to characterize

One withdrawn nomination included two CoAs for AOD-9604 acetate, from Darmerica and Biopeptek. The CoA from Darmerica indicated that microbial limits/bacterial endotoxin levels are not controlled, in addition to impurities. Microbial limits are not controlled in Biopeptek's CoA.

Conclusions: AOD-9604 acetate is an acetic acid salt form of AOD-9604 (free base). AOD-9604 (free base) is a 16-amino acid peptide with a disulfide bond between two cysteines at position 7 and 14. The presence of this disulfide bridge can lead to degradation by reducing the disulfide bond and aggregate formation (Janvier et al. 2018a; Janvier et al. 2018b).

AOD-9604 acetate is considered to be not physically and chemically well characterized because certain critical characterization data specific to AOD-964 (free base), such as potential peptide impurities, were not found in publicly available scientific literature and the provided CoAs. Specific tests for AOD-9604 acetate are not available in the public domain as well as in the submitted CoAs, such as tests for specific impurities, aggregates, and microbial test. As discussed in Section II.D.2.d, FDA is concerned about the potential for immunogenicity of AOD-9604 acetate when formulated in an injectable dosage form for SC administration due to the potential for aggregation as well as potential peptide-related impurities, as discussed in the impurities section. Injectable routes of administration may present a particular risk for immunogenicity. We also note that the stability, pharmacological activity, and immunogenic properties of peptides such as AOD-9604 acetate are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

[20] https://particlepeptides.com/en/buy-peptides/9-aod-9604-5mg.html. Accessed 5/27/24.

In addition, the nominators proposed transdermal cream and/or oral capsule as anticipated pharmaceutical dosage forms, in which polymorphism of the BDS is a critical attribute to ensure the efficacy of the compounded/finished drug product. However, information regarding the polymorphism of AOD-9604 acetate is not available in the nomination packages as well as in the literature.

B. Has the substance been used historically in compounding?

This evaluation focuses on AOD-9604 (free base) and AOD-9604 acetate, also referred to as "anti-obesity drug" or "advanced obesity drug" on certain websites[21], for SC injection, transdermal cream, and oral capsule, and its use in patients with obesity; however, FDA looked generally for information on the historical use of AOD-9604 (free base) and AOD-9604 acetate in compounding. Information about use may not specify specific attributes of the product, such as route of administration. Databases searched for information on both substances for this evaluation included PubMed, EMBASE, Google/Google Scholar, Natural Medicines, GlobalEdge, Cochrane Library, United States Pharmacopeia – National Formulary, European Pharmacopoeia, Chinese Pharmacopoeia, Indian Pharmacopoeia, and Japanese Pharmacopoeia. It is often unclear whether the AOD-9604 discussed in this section is the salt formulation or the free base and whether it was compounded or not. Therefore, FDA will consider the information discussed in this section in its evaluation of both the free base and salt form as appropriate.

1. Length of time the substance has been used in compounding

The withdrawn nominations did not provide historical use data. Literature shows that AOD-9604 was first developed and patented by Metabolic Pharmaceuticals in the late 1990s (Wilding 2004). Although AOD-9604 has been used in the past, there is insufficient information to determine how long it has been used in compounding. According to outsourcing facility (OF) reports submitted to FDA between 2017 and 2023, no OFs reported compounding any drug products containing AOD-9604.[22]

2. The medical condition(s) it has been used to treat

AOD-9604 is a peptide that was originally developed for obesity treatment. However, it "did not show a clinically meaningful weight loss outcome across the trial population" (Cox et al. 2015).

Results from a Google search using the terms *AOD-9604 compounding, AOD-9604 acetate compounding, AOD-9604 compounding pharmacy, AOD-9604 acetate compounding, or AOD-*

[21] Forward Healthy Lifestyles clinic: https://www.forwardhealthylifestyles.com/weight-loss-procedures-germantown/aod-9604-peptide/, Elite Plastic Surgery: https://eliteplasticsurgeryaz.com/peptide-hormone-therapy/, and Mobile Care Health clinic: Exclusive concierge medicine https://mobilecarehealth.shop/product/aod-9604/. Accessed 03/07/24.

[22] 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/index.cfm.

9604 compounding pharmacy 503A show that a compounding pharmacy website recently marketed AOD-9604, as an injectable formulation, for various uses including to increase weight loss, boost metabolism, help with obesity, and control diabetes.[23]

FDA identified numerous clinics such as wellness clinics and medical spas that market products containing AOD-9604 for various uses including osteoarthritis, osteoporosis, worn cartilage, bone damage, hypercholesteremia, diabetes, depression, anti-aging, skin care, boost metabolism, and support weight loss.[24] AOD-9604 products are also marketed to enhance muscle-building, reduce body fat, stimulate lipolysis, inhibit lipogenesis, trigger fat release, and increase calorie burn. In addition, clinics also claim that AOD-9604 products as not negatively affecting tissue growth, containing regenerative properties, and helping with cartilage and bone repair especially when paired with the peptide BPC (body protection compound).[25] Some wellness clinic websites recommend that the peptide is to be injected 30 minutes prior to eating to fully metabolize and achieve optimal results.[26]

3. How widespread its use has been

According to FDA OF reporting data from January 2017 to December 2023, there were no reported compounded drug products containing AOD-9604.[27] However, a Google search indicated that a compounding pharmacy recently marketed AOD-9604 as a 1000 mcg/mL injectable vial.[28]

A Google search indicates that products containing AOD-9604 are widely advertised in the U.S. by medical spas (med spas)/wellness clinics, and medical concierge services. Although websites often do not describe or clearly state that the AOD-9604 product is compounded, this is likely to be the case considering that there are no FDA-approved drug products containing AOD-9604 free base (or AOD-9604 acetate). One of the wellness clinics indicated that "peptides are

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[23] American Wellness Pharmacy: https://americanwellnesspharmacy.com/compounding-pharmacy-las-vegas/. Accessed 3/11/24. See Appendix 1

[24] Elite Plastic Surgery: https://eliteplasticsurgeryaz.com/peptide-hormone-therapy/, American Medical Wellness: https://www.americanmedicalwellness.com/services-fat-burning-peptide-therapy/,Mobile Care Health clinic: Exclusive concierge medicine https://mobilecarehealth.shop/product/aod-9604/, Regenics: https://regenics.com/products/aod-9604/, and Lowcountry male: https://lowcountrymale.com/aod-9604-peptide-therapy/. See Appendix 3. Accessed 3/11/24.

[25] AgeRejuvenation Medical Spa: https://agerejuvenation.com/peptide-aod-9604/, Revitalized Health https://rhsupplements.com/aod-9604, and Forward Healthy Lifestyles clinic: https://www.forwardhealthylifestyles.com/weight-loss-procedures-germantown/aod-9604-peptide/. Accessed 3/7/24.

[26] American Medical Wellness: https://www.americanmedicalwellness.com/services-fat-burning-peptide-therapy/, Renew vitality testosterone clinic: https://www.vitalityhrt.com/blog/aod-9604-peptide-therapy/, Lowcountry male: https://lowcountrymale.com/aod-9604-peptide-therapy/, See Appendix 3 , and Age Rejuvenation Medical Spa: https://agerejuvenation.com/peptide-aod-9604/. Accessed 3/11/24.

[27] Wayback Reporting. https://wayback.archive-it.org/7993/20190423031057/https:/www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm393571.htm, https://wayback.archive-it.org/7993/20171114123637/https:/www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm393571.htm, and https://www.accessdata.fda.gov/scripts/cder/outsourcingfacility/index.cfm .

[28] American Wellness Pharmacy: https://americanwellnesspharmacy.com/compounding-pharmacy-las-vegas/. Accessed 3/11/24. See Appendix 1

prepared and delivered to your doorstep from a 503B compounding pharmacy".[29] One wellness clinic website states, the "peptide is no longer available due to it being placed on the FDA's list".[30]

AOD-9604 products in several dosage forms are marketed by these clinics. Most clinics offer AOD-9604 products either as SC injections or oral formulations (tablets, capsules, or troches). One wellness clinic website markets AOD-9604 products as a 600 mcg/ml 10 mL vial and a 1 mg capsule.[31] Another wellness clinic website markets a product containing AOD-9604 acetate as 250 mcg rapid ODT daily.[32] Clinics are marketing products containing AOD-9604 in combination with other APIs such as aminophylline, glycyrrhizic acid, and N-acetyl BPC-157 as injectable formulations and are marketing products containing AOD-9604 in combination with topiramate, naltrexone, and methionine inositol choline (MIC) as an oral formulation.[33]

AOD-9604 has been used in sports as a doping agent. A report released by the Australian Crime Commission listed AOD-9604 as a peptide supplied to athletes and football players admitted to its use. Also, unlabeled vials containing AOD-9604 were obtained from German and Belgian elite athletes. Furthermore, in the USA, AOD-9604 has been detected in confiscated vials (Cox et al. 2015). AOD-9604 is on the list of prohibited substances under section S2.2 of the World Anti-Doping Agency (WADA).[34]

4. Recognition of the substance in other countries or foreign pharmacopeias

A search of the National Medical Registries, European Medicines Agency website, European Pharmacopoeia (11.5 Edition), Chinese Pharmacopoeia (10th Edition, 2015), Indian Pharmacopoeia (2010), and the Japanese Pharmacopoeia (18th Edition) did not show any monograph listings for either AOD-9604 or AOD-9604 acetate. The Australian government Advisory Committee on Medicines Scheduling (ACMS) recommended, and confirmed, adding AOD-9604 to the poisons standards, under performance and image enhancing drugs (PIEDs) for which possession without authority is illegal (e.g., possession other than in accordance with a legal prescription).[35]

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[29] Prefusion Health: https://www.prefusionhealth.com/peptide-therapy. Accessed 3/7/24.
[30] Renew vitality testosterone clinic: https://www.vitalityhrt.com/blog/aod-9604-peptide-therapy/. Accessed 3/8/24.
[31] Mobile Care Health clinic: Exclusive concierge medicine https://mobilecarehealth.shop/product/aod-9604/. Accessed 3/8/24.
[32] Regen Doctors: https://regendoctors.com/products/aod-9604-acetate-250-mcg-rapid-odt-30-melts-1-daily/. Accessed 5/30/24. See Appendix 2
[33] Mobile Care Health clinic: Exclusive concierge medicine https://mobilecarehealth.shop/product/aod-9604/, and Thrive Health Solutions clinic https://thrivecolorado.com/thrive-about-us/. Accessed 3/8/24.
[34] WADA was established in 1999 as an international independent agency to lead a collaborative worldwide movement for doping-free sport. See https://www.wada-ama.org/en/who-we-are. WADA, 2022, Prohibited Substances, World Anti-Doping Agency Prohibited List. See https://www.wada-ama.org/sites/default/files/2023-05/2023list_en_final_9_september_2022.pdf. Accessed 3/7/24.
[35] The website did not specify the form of AOD-9604 (i.e., AOD-9604 acetate or AOD-9604 (free base)). See Australian Government performance and image enhancing drugs https://www.tga.gov.au/resources/publication/scheduling-decisions-interim/scheduling-delegates-interim-decisions-and-invitation-further-comment-accsacms-february-2016/27-performance-and-image-enhancing-drugs. Accessed 06/07/24. The Australian Poisons Standard is a record of classification of medicines and chemicals into Schedules for inclusion in the relevant legislation of the States and Territories. There are 10 Schedules that have increasingly

Conclusions: Available literature indicates that AOD-9604 was first developed in the late 1990s. The length of time and extent to which AOD-9604 has been used in compounding is unclear, however, there is some evidence of the use of AOD-9604 in compounding human drug products. AOD-9604 has been studied for use in obesity. It has also been marketed for use in osteoarthritis, osteoporosis, worn cartilage, bone damage, hypercholesteremia, diabetes, depression, anti-aging, skin care, boosting metabolism, and supporting weight loss. In the sources considered for this section, it is often unclear whether the AOD-9604 discussed is the salt form or the free base. Based on OF reporting data, OFs have not reported compounding any drug products containing AOD-9604 or AOD-9604 acetate. Internet search results show that compounders have prepared AOD-9604 in injectable and oral formulations. These formulations are being marketed by medical spas and wellness clinics.

C. Are there concerns about whether a substance is effective for a particular use?

The following databases were consulted in the preparation of this section: PubMed, Embase, ClinicalTrials.gov, DailyMed, Drugs@FDA, relevant professional healthcare organization websites, and various online clinical references and websites such as information from National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC). In addition to a review of pertinent information from these databases, this section provides a brief overview and a discussion of the use evaluated, obesity.

The clinical references submitted by the nominators and those identified by FDA do not clearly identify whether the AOD-9604 in products administered in the clinical studies was a salt or the free base. Therefore, throughout this section, the substance will be generally referred to as AOD-9604 unless otherwise specified as free base or acetate salt.

AOD-9604 related BDSs were nominated for the following uses: "weight loss, osteoporosis, and osteoarthritis." FDA did not evaluate the proposed uses of osteoporosis and osteoarthritis because the nominations did not include sufficient information for FDA to evaluate whether the substance is appropriate for these uses in compounded drug products, and FDA did not identify clinical studies using AOD-9604 related BDSs in these populations in its own literature search.

The nominators nominated AOD-9604 related BDSs for use in "weight loss." However, based on references cited by the nominators, the population studied was subjects with obesity. In addition, obesity is a chronic complex disease[36] while the term "weight loss" is one of the goals for its treatment. Therefore, we will evaluate obesity.

1. Obesity

restrictive regulatory controls with progression from Schedule 1 through 10. There are also 13 Appendices which describe exemptions or additional restrictions placed on some substances. See https://www.legislation.gov.au/F2024L00095/latest/text. Accessed 6/7/24.

[36] See World Health Organization: Obesity and overweight, accessed 9/16/24 https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight#:~:text=Overweight%20is%20a%20condition%20of,the%20risk%20of%20certain%20cancers

Obesity is defined by the increase in size and amount of fat cells in the body. Obesity is a chronic health condition that increases the risk for heart disease and is linked to other health problems, such as type 2 diabetes and cancer. Risk factors for obesity include lack of physical activity, unhealthy eating behaviors, insufficient good-quality sleep, stress, chronic health conditions, genetics, certain medications, and one's environment. Overweight is a condition of excessive fat deposits.[37] Diagnosis may be based on medical history and high body mass index (BMI). For adults, healthy weight is a BMI of 18.5 to 24.9 kg/m^2, overweight as BMI 25 to 29.9 kg/m^2 and obesity as BMI $\geq$ 30 kg/m^2.[38,39] The medical rationale for weight loss through weight management in patients with obesity or in overweight patients is to decrease the risk of mortality and other health risks including type 2 diabetes mellitus, hypertension, dyslipidemia, and coronary heart disease.[40] Treatment options include lifestyle modifications, pharmacologic therapy, and/or surgery.

The Endocrine Society Clinical Practice Guideline[41] on the pharmacological management of obesity recommends that diet, exercise, and behavioral modification be included in all weight management approaches for BMI $\geq$ 25 kg/m^2 and that other tools such as pharmacotherapy (BMI $\geq$ 27 kg/m^2 with comorbidity or BMI over 30 kg/m^2) and bariatric surgery (BMI $\geq$ 35 kg/m^2 with comorbidity or BMI over 40 kg/m^2) be used as adjuncts to therapy. The guideline states that "patients unable to successfully lose and maintain a goal weight may be candidates for weight loss medications if they meet the criteria on the drug's label." Treatment with products containing AOD-9604 is not mentioned in the clinical practice guidelines.

a. Reports of trials, clinical evidence, and anecdotal reports of effectiveness, or lack of effectiveness, of the bulk drug substance

Both nominators cited Stier et al. 2013, which presented a summary of the clinical safety data on AOD-9604 in subjects with obesity; the reference did not report data on effectiveness. This reference will be discussed in detail in the safety section II.D.2.c.

Both nominators also cited Khan et al. 2012, a review article that summarized 21 drugs currently used in obesity and new compounds under clinical development, including AOD-9604. The article includes a paragraph describing (in-vitro) mechanism of action of AOD-9604 being developed by the Australian company Metabolic Pharmaceuticals Limited. The reference did not include data on clinical effectiveness.

The nominations did not include, and we did not identify human exposure data on this substance administered via two of the proposed routes of administration (ROAs), SC or topical.

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[37] Ibid.
[38] See: Overweight and Obesity. NIH National Heart, Lung, and Blood Institute, accessed 5/22/24, https://www.nhlbi.nih.gov/health/overweight-and-obesity.
[39] See: Guidance for Industry Developing Products for Weight Management, accessed 9/16/24, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/developing-products-weight-management-revision-1
[40] Ibid.
[41] See: Pharmacological Management of Obesity Guideline Resources, Endocrine Society, accessed 6/4/24, https://www.endocrine.org/clinical-practice-guidelines/pharmacological-management-of-obesity

Our search of published medical literature retrieved three additional references that include information on effectiveness of products containing AOD-9604 in intravenous (IV) and oral ROAs.

- Wilding 2004 describes preclinical and clinical development of AOD-9604 (by Metabolic Pharmaceutical Ltd., Australia) for the potential treatment of obesity. Three clinical studies briefly described in the publication are described below.[42]

  In a double blind (DB), dose-escalation study, 23 adults with obesity (mean BMI of 42.3 kg/m^2) received single doses of IV AOD-9604 (25, 50 or 100 mcg/kg) or placebo, once weekly for 4 weeks. Per author, "the concentration of non-esterified fatty acid (NEFA), a marker of fat metabolic changes that are expected to result in weight loss, increased in these patients after 2 hours." The author added, some weight loss occurred, on average 0.58 kg over 3 weeks, but this was not statistically different from placebo.[43]

  A trial in 16 men with obesity (average BMI of 41.3 kg/m^2) received once weekly doses of oral AOD-9604 (9, 27 and 54 mg) or placebo for 4 weeks. Per author, "At 4 hours, a rise in NEFA was again observed at all dose levels; there was no statistically significant weight loss compared with placebo."[44]

  A DB, dose escalation study in 36 men with obesity were randomized to receive either AOD-9604 (10, 30 or 60 mg) or placebo for 1 week ROA not specified by author). Average weight loss over 1 week at the 10-mg dose was reported to be 1 kg compared with 0.6 kg in the placebo group. Per author, "the other doses appeared less effective, suggesting an optimal dose of 10 mg or lower." No additional details were provided in the publication.[45]

  Per author, the clinical studies do not show any statistically significant weight loss when AOD-9604 was administered to patients with obesity compared to placebo. This publication provided limited information such as insufficient details about methodology and study results. Limitations of the studies include small sample size, unclear study parameters and limited numerical information on the findings.[46]

- Herd et al. 2005 is an abstract from an annual scientific meeting program that described a DB, randomized, placebo-controlled, study in 300 patients with obesity ("otherwise healthy males and females", 30 to 65 years old) randomized after a 2-week run-in period to receive oral AOD-9604 (1, 5, 10, 20 or 30 mg per day) or placebo for 12 weeks. Authors state

[42] We note that based on the study description and references in this publication, these are the same three studies described in a reference cited by the nominator (Stier et al. 2013), see section II.D.2.c.
[43] We note that this study appears to be the same as METAOD002 described in Stier et al. 2013 discussed in section III.D.2.c.
[44] We note that this study appears to be the same as METAOD003 described in Stier et al. 2013 discussed in section III.D.2.c.
[45] We note that this study appears to be the same as METAOD004 described in Stier et al. 2013 discussed in section III.D.2.c.
[46] We note the references used in this publication were press releases from the pharmaceutical company formally developing AOD-9604 which are no longer available.

"Weight loss over 12 weeks was greater in the response to all doses of AOD-9604 than placebo, with a non-linear dose response. The largest effect occurred in the 1 mg dose and was 'significant' for females." The mean rate of weight loss was: 1 mg -0.22 kg/week, 20 mg -0.13 kg/week, or 30 mg -0.15 kg/week compared to placebo -0.07 kg/week; no details were provided on weight loss in the 5 mg and 10 mg groups. Authors added, "mean weekly rate of reduction in waist circumference was statistically significant at all doses of AOD-9604 compared to placebo…small reduction in total cholesterol and LDL levels, and a lower incidence of diabetes at the end of the treatment period." No details of measurements or laboratory values were provided. Authors concluded, "daily oral administration of AOD-9604 is safe and well tolerated and promotes weight and waistline reduction" and that dose response is complex, with both low dose and high dose effects, and differential effects between men and women. We note that the authors claim of weight reduction is based on small differences between the treatment and placebo groups which has unclear meaningful therapeutic effects. Interpretation of this study is limited by the minimal data in the abstract including insufficient details about the study methodology and results.[47] We did not locate a publication of the study methods and results.

- AOD-9604 was developed by Metabolic Pharmaceuticals Ltd. in Australia for the treatment of obesity. On February 21, 2007, Metabolic Pharmaceuticals Ltd publicly announced[48] "that the Phase 2B trial results for its drug, *AOD9604,* do not support the commercial viability of the drug as a treatment for obesity. Development of the drug for this condition is terminated."

  A submission to the Australian Stock Exchange and Australian Security and Investment Commission provided additional details of the OPTIONS Study[49] trial design:

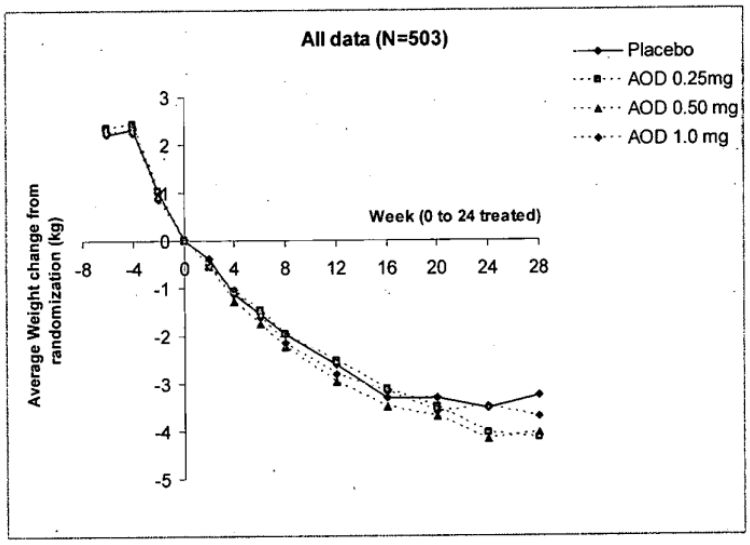
  > A randomized (R), placebo-controlled (PC), DB trial, in adults (536 enrolled; 502 randomized) with obesity (18-65 years old, BMI 30-45 kg/m^2). Study subjects received oral AOD-9604 (0.25, 0.5, or 1 mg) or placebo once daily in addition to a dietician-supervised diet and exercise program for 24 weeks. The primary endpoints were (1) statistically significant weight loss after 12 weeks of treatment for any one of three daily AOD-9604 doses compared to placebo, and (2) safety and tolerability. According to the authors, the trial was powered for an 80% chance of achieving significance on the primary endpoint if the weight loss compared to placebo was 1.8 kg. The trial also evaluated secondary endpoints (weight loss over 24-week period, comparison of effects of the different doses, waistline reduction, body fat reduction, and improvement of risk factors). Trial findings (included in the figure below) indicate there was not a significant difference in the primary endpoint of weight loss between placebo and AOD-9604.

[47] We note that this study appears to be the same as METAOD005 described in Stier et al. 2013 discussed in section III.D.2.c

[48] See: Metabolic Pharmaceutical Limited submission of information filed with Australian Stock Exchange and Australian Securities and Investment Commission. Relevant pages on Announcements on pages 5/53-10/53. Accessed 9/12/24. https://www.sec.gov/Archives/edgar/vprr/0702/07021963.pdf

[49] We note that this study appears to be the same as METAOD006 described in Stier et al. 2013 discussed in section III.D.2.c.

Figure 3. The OPTIONS Study Trial Data Results[50]



The company further stated that, "Trial results showed that weight loss compared to placebo at the primary and secondary endpoints of 12 or 24 weeks of treatment, was too low to reach statistical significance. The design of the obesity trial included Phase 3 conditions, such as a broader population of subjects (536 in total) and a formal diet and exercise program. Under these additional conditions the AOD9604 treatment did not demonstrate the weight loss required to support commercial outcomes….the overall population did not respond consistently…" It does not appear that this study was published in the medical literature, specifically, details of the study design and preliminary efficacy results.

A search of clinicaltrials.gov did not list any studies on AOD-9604.

b. Whether the product compounded with this bulk drug substance is intended to be used in a serious or life-threatening disease

Obesity increases the risk for many serious diseases and health conditions such as type 2 diabetes, heart disease, stroke, and certain types of cancers.[51]

c. Therapies that have been used for the conditions(s) under consideration

There are FDA-approved drug products that treat the same medical condition as that proposed for the AOD-9604 compounded drug product(s).[52] The following list includes FDA-approved drug products indicated for use as adjunctive therapy for weight management in obesity.

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[50] See: Metabolic Pharmaceutical Limited submission of information filed with Australian Stock Exchange and Australian Securities and Investment Commission. Relevant pages on Announcements on pages 5/53-10/53. Accessed 9/12/24. https://www.sec.gov/Archives/edgar/vprr/0702/07021963.pdf

[51] See: Health Effects of Overweight and Obesity. CDC website, accessed 11/09/23, https://www.cdc.gov/healthyweight/effects/index.html.

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

- Glucagon-like peptide-1 (GLP-1) receptor agonist (e.g., liraglutide [Saxenda SC injection[53]], semaglutide [Wegovy SC injection[54]])
- Glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 receptor agonist (e.g., tirzepatide [Zepbound SC injection[55]])
- Naltrexone HCl and bupropion HCl (e.g., Contrave[56] extended-release oral tablets), an opioid antagonist (naltrexone) and an aminoketone antidepressant (bupropion)
- Inhibitor of gastrointestinal lipases orlistat (e.g., Xenical 120 mg oral capsules[57]), (e.g., Alli 60 mg OTC[58])
- Phentermine and topiramate (e.g., Qsymia oral capsules[59]), a sympathomimetic amine anorectic (phentermine) with a sulfamate-substituted monosaccharide (topiramate)

Conclusions: Based on available data, there is a lack of evidence to support the effectiveness of AOD-9604 (free base) and AOD-9604 acetate for the treatment of obesity for any ROA. Clinical practice guidelines for health professionals do not mention AOD-9604 (free base) or AOD-9604 acetate for the treatment of obesity. The available information is limited to short summaries of clinical studies on the administration of oral or intravenous AOD-9604 which lack sufficient details about methodology and results. In most of the studies we identified, AOD-9604 failed to show benefit for weight reduction when compared to placebo. Importantly, a study conducted by Metabolic Pharmaceuticals Ltd. in Australia enrolled 536 patients with obesity and did not find a significant difference in weight loss after 12 weeks (the primary endpoint) with AOD-6904 treatment compared to placebo. The company terminated development of the drug for obesity because of the failure of the study. The nomination did not include, and FDA did not find, information on products containing AOD-9604 (free base) or AOD-9604 acetate administered by the subcutaneous or transdermal routes of administration in humans. Obesity increases the risk for many serious diseases and health conditions, and there are multiple FDA-approved drug products for use in weight management in patients with obesity.

D. Are there concerns about the safety of the substance for use in compounding?

1. Nonclinical Assessment

[53] See, e.g., label for Saxenda (liraglutide), NDA 206321/S-16. Drugs@FDA, accessed 5/14/24, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=206321.
[54] See, e.g., label for Wegovy® (semaglutide), NDA 215256/S-7. Drugs@FDA, accessed 5/14/24, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=215256.
[55] See label for Zepbound (tirzepatide), NDA 217806. Drugs@FDA, accessed 5/14/24, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=217806.
[56] See label for Contrave (naltrexone hydrochloride and bupropion hydrochloride), NDA 200063/S-21. Drugs@FDA, accessed 5/14/24, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=200063.
[57] See label for Xenical (orlistat), NDA 020766/S-3
8. Drugs@FDA, accessed 5/14/24, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=020766.
[58] See label for over-the-counter (OTC) Alli (orlistat), NDA 021887. Drugs@FDA, accessed 5/14/24, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021887
[59] See label for Qsymia (phentermine and topiramate), NDA 022580/S-23. Drugs@FDA, accessed 5/14/24, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=022580.

The nominators submitted nonclinical information. Specifically, they submitted a list of seven published articles. Five articles describe the pharmacological effects of AOD-9604 in different animal models (Heffernan et al. 2001a; Heffernan et al. 2001b; Khan et al. 2012; Kwon and Park 2015; Mayer et al. 2009), and one article describes experiments conducted to characterize the toxicological profile of AOD-9604 (Moré and Kenley 2014). One article describes the pharmacological effects of a different peptide – AOD-9401 – on lipid metabolism of obese mice (Heffernan et al. 2000); this peptide is out of the scope of this evaluation, and this article is not discussed further.

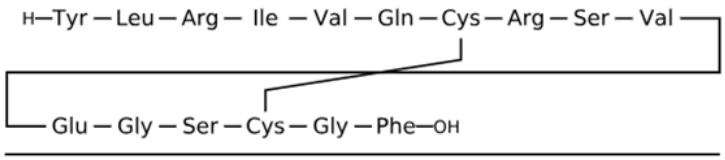
The following databases were consulted in preparation of this section: Drugs@FDA, Embase, European Chemicals Agency, FDA's Generally Recognized as Safe (GRAS) Notice Inventory, Google, Google Scholar, National Institutes of Health's dietary supplement label database, National Toxicology Program website,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

The nonclinical articles submitted by the nominators and those identified by FDA do not always clearly identify AOD-9604 as free base or salt. Therefore, in this section, the substance will be generally referred to as AOD-9604, unless the article under discussion clearly specifies the use of the free base or the acetate salt.

a. General pharmacology of the drug substance

As discussed earlier in this evaluation, AOD-9604, the active moiety of AOD-9604 (free base) and AOD-9604 acetate, is a synthetic cyclic peptide that consists of the amino acid sequence 177-191 of the hGH with an additional tyrosine at the C-terminal (Figure 4).

Figure 4. Amino Acid Sequence of AOD-9604.



Arg: arginine; Cys: cysteine; Gly: glycine; Glu: glutamic acid; Ile: isoleucine; Leu: leucine; Phe: phenylalanine; Ser: serine; Tyr: tyrosine. Source: AOD9604 acetate | C80H127N23O25S2 | CID 156599045 - PubChem (nih.gov)

As discussed in the next two paragraphs, nonclinical pharmacological studies have reported that, like hGH, AOD-9604 reduces lipogenesis and increases lipolysis and fatty acid oxidation in obese rodents (Heffernan et al. 2001a; Heffernan et al. 2001b; Ng et al. 2000). In these studies, the authors list report dissolving AOD-9604 in saline.

In one pharmacological study, adult obese male and female Zucker rats were treated with AOD-9604 (500 µg/kg/day, oral gavage), hGH (70 µg/kg/day, oral gavage), or vehicle (saline) for 21 days (Ng et al. 2000). Obese rats treated with AOD-9604 or hGH gained approximately 50% less body weight and had significantly higher lipolytic activity in adipose tissue than rats treated with vehicle (Ng et al. 2000). While treatment with hGH induced insulin resistance in obese Zucker rats, treatment with AOD-9604 had no effect on the insulin sensitivity of the rats (Ng et al. 2000).

In two other pharmacological studies, 3-month-old male obese (*ob/ob*) mice were subjected to 14-day treatments with AOD-9604 (250 μg/kg/day), hGH (1 mg/kg/day), or saline delivered as continuous infusions via subcutaneously implanted osmotic minipumps or as daily intraperitoneal (IP) injections (Heffernan et al. 2001a; Heffernan et al. 2001b). Obese mice treated with AOD-9604 or hGH gained ~5-10% less body weight than vehicle-treated mice (Heffernan et al. 2001a; Heffernan et al. 2001b). The reduced body weight gain of AOD-9604-treated mice was not due to reduced feed consumption and was accompanied by: (i) increased in-vivo fat oxidation (assessed by indirect calorimetry), (ii) increased plasma glycerol levels (an index of lipolysis), and (iii) reduced white and brown adipose tissue (Heffernan et al. 2001a; Heffernan et al. 2001b). In contrast to hGH, AOD9604 had no apparent effect on glycemia, insulin secretion, or insulin sensitivity. For instance, in obese (*ob/ob*) mice, hGH significantly increased plasma glucose levels, reduced plasma insulin levels, and reduced glucose oxidation (Heffernan et al. 2001b). By contrast, AOD-9604 had no significant effect on plasma glucose levels, plasma insulin levels, or glucose oxidation (Heffernan et al. 2001a).

The lipolytic and diabetogenic effects of GH are thought to be mediated by its ability to interact with and activate GH receptors (GHRs) expressed in different cells. Specifically, GH-induced activation of GHRs in adipocytes increases lipolysis by: (i) increasing expression and inducing activation of hormone-sensitive lipase (HSL), an enzyme that catalyzes the breakdown of adipocyte lipids into free fatty acids (FFAs) and glycerol, and (ii) reducing expression of fat specific protein 27 (FSP27), a negative regulator of lipolysis (Kopchick et al. 2020; Sharma et al. 2018). GH-induced GHR activation in hepatocytes and skeletal muscle cells facilitates uptake of amino acids, reduces cellular uptake of glucose, and stimulates both gluconeogenesis and glycogenolysis, thereby, increasing the production of glucose. The net effect of GH on glycemia is complex in part because GH, acting via GHRs, also increases expression of insulin-like growth factor-1 (IGF-1), which has insulin-like properties. Long-term exposures of rodents to higher-than-physiological GH levels induce insulin resistance (Ng et al. 2000), and long-term treatment of humans with GH is generally associated with hyperglycemia and insulin resistance (Bramnert et al. 2003; Kim and Park 2017).

Although AOD-9604 is a fragment of the C-terminal domain of hGH, different lines of evidence suggest that GHRs are unlikely to mediate the lipolytic effects of AOD-9604 (Heffernan et al. 2001b). First, at concentrations ranging from 0.1 pM to 10 nM, hGH displaces ^{125}I-hGH binding from GHRs ectopically expressed in Ba/F3 cells. By contrast, at the same concentrations, AOD-9604 has no effect on ^{125}I-hGH binding to GHRs. In addition, at concentrations ranging from 0.1 pM to 0.1 mM, hGH increases proliferation of GHR-expressing Ba/F3 cells. By contrast, at the same concentrations, AOD-9604 has no effect on the proliferation of GHR-expressing Ba/F3 cells (Heffernan et al. 2001b). Some authors also claim that, in contrast to GH, AOD-9604 does not increase expression of IGF-1 (Kwon and Park 2015). However, FDA has not identified nonclinical data to support this claim.

The molecular target(s) and the mechanism(s) of action underlying the pharmacological effects of AOD-9604 remain unknown. Findings from a pharmacological study conducted in mice with a null mutation in the gene that encodes β3 adrenergic receptors, whose activation in adipocytes is known to lead to lipolysis (Mottillo et al. 2014), suggested that the lipolytic effects of AOD-

9604 depend, at least in part, on intact β3 adrenergic receptor signaling (Heffernan et al. 2001a). Specifically, the study authors reported that in mice with a null mutation of the β3 adrenergic receptor-encoding gene, 14-day treatment with AOD-9604 (250 μg/kg/day, IP) had no effect on body weight gain, size of epididymal white and brown adipose tissues, and plasma glycerol levels (Heffernan et al. 2001a). In addition, the authors reported that treatment of wild-type obese mice with AOD-9604 increased expression of β3 adrenergic receptors in white and brown adipose tissues (Heffernan et al. 2001a).

Findings from the studies discussed above should be interpreted with caution because none of the studies assessed dose-response relationships for AOD-9604 to induce body weight loss and lipolysis. In addition, statistical treatment of the data in all studies was not corrected for multiple comparisons, thereby creating uncertainty of the statistical significance of the findings. Finally, the molecular targets for AOD-9604 have not been identified and its mechanisms of action remain unknown, making it difficult to assess the biological plausibility of the pharmacological effects reported in the studies.

b. Pharmacokinetics/Toxicokinetics (TK)

A pharmacokinetic study was conducted in adult female pigs treated intravenously or orally with AOD-9604. At various times after the treatments, blood was drawn from the animals, and plasma concentrations of AOD-9604 were measured by means of liquid chromatography with tandem mass spectroscopy (Moré and Kenley 2014).

In pigs treated with the intravenous (IV) bolus dose of AOD-9604 (400 μg/kg), the half-life ($t_{1/2}$) of the peptide was found to be very short (~3 min) (Moré and Kenley 2014). In the AOD-9604-treated pigs, the mean maximal plasma concentration (C_{max}) of AOD-9604 was 1,944 ng/mL and the mean area-under-the-curve (AUC) of plasma concentration vs time expressed as mean ± standard deviation was 12,743 ± 625 ng/mL/min (Moré and Kenley 2014).

In pigs treated with an oral dose of 2 mg/kg, AOD-9604 appeared to be well absorbed, and its plasma concentrations peaked at approximately 60 min after dosing. The mean C_{max} and AUC in pigs treated orally with an AOD-9604 dose of 2 mg/kg were 1,127 ng/mL and 108,630 ± 32,654 ng/mL/min, respectively. The ratio of the dose-adjusted AUCs generated by the oral and IV treatments would result in an oral bioavailability of 170%, which unrealistically exceeds the theoretical maximal 100%, for AOD-9604 (Moré and Kenley 2014). The authors suggested that the high variability of the data was likely to account for the unrealistic high oral bioavailability. We further note that many measurements from plasma of orally treated pigs had standard deviations that were nearly 100% of the mean. Therefore, the magnitude of the oral bioavailability of AOD-9604 remains unclear.

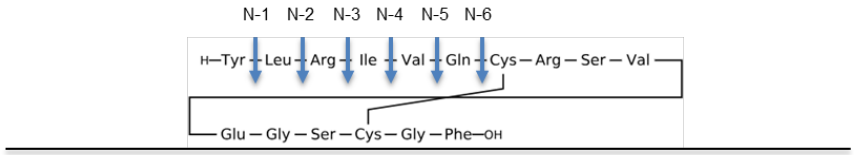
The oral bioavailability of AOD-9604 does not seem to be specific to pigs because, as discussed in section D.1.a, AOD-9604 administered orally to rats was reported to be pharmacologically active (Ng et al. 2000). No study has identified the exact molecular features that could explain the stability of AOD-9604 in and its absorption from the gastrointestinal tract. However, there are reports that large peptides made cyclic by the incorporation of cysteine residues that can form intramolecular disulfide bonds tend to be more resistant to enzymatic degradation and can be

more readily taken up by cells than the corresponding cysteine-free linear peptide sequences (e.g., Al Musaimi et al. 2022).

Tissue distribution of AOD-9604 was assessed by whole-body autography in rats that were treated intravenously with radioactively (^{14}C) labeled AOD-9604 (Moré and Kenley 2014). The authors reported that, 5 min after the IV injection of ^{14}C-AOD-9604 (5 mg/kg) in rats, radioactivity was detected mostly in the pancreas, the pineal body, the thyroid, and the kidney cortex. They also reported that, when ^{14}C-AOD-9604 (5 mg/kg) was delivered to rats by oral gavage, radioactivity in the tissues reached a peak at about 30 min after dosing, with radioactivity tissue distribution being similar to that seen after the IV injection (Moré and Kenley 2014). We note that the authors do not report whether the measured tissue radioactivity was due to the intact AOD-9604 peptide or radioactively labeled metabolites of the peptide, making it difficult to assess the true tissue distribution of the intact peptide.

Moré and Kenley (2014) reported that, during a 1-h incubation of rat blood with AOD-9604 at room temperature, AOD-9604 was quickly hydrolyzed by successive amino-terminal truncation, as illustrated in Figure 5. In blood, the in-vitro $t_{1/2}$ of the AOD-9604 was 4 min, and AOD-9604 was fully hydrolyzed in 56 min.

Figure 5. N-Amino Truncation Sites (N-1 through N-6) of AOD-9604 Incubated with Rat Blood In Vitro [Reviewer-Generated Figure].



AOD-9604 truncation at sites 1 through 6 from the N-terminus (marked by blue arrows) releases shorter peptides with minus 1, minus 2, minus 3, minus 4, minus 5, and minus 6 amino acids (More and Kenley 2014). **Note**: The authors did not publish the data to demonstrate the amino acid sequence of the shorter peptides.

The authors identified the same truncated peptides in the plasma of pigs that had been treated orally or intravenously with AOD-9604 (Moré and Kenley 2014). Following oral treatment, the N-2 and N-3 peptides were the main degradation products of AOD-9604. Following IV treatment, the N-5 and N-6 peptides were the main degradation products of AOD-9604.

At the time of this evaluation, the nominator did not submit, and FDA did not identify nonclinical studies to characterize the pharmacokinetic profile of AOD-9604 (free base) or AOD-9604 acetate, particularly its absolute bioavailability via the nominated ROAs (SC and transdermal).

c. Acute toxicity[60]

At the time of this evaluation, the nominator did not submit, and FDA did not identify nonclinical acute toxicity studies of AOD-9604 (free base) or AOD-9604 acetate.

[60] 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*

d. Repeat-dose toxicity[61]

At the time of this evaluation, the nominators submitted one article reporting toxicological studies conducted with AOD-9604 (Moré and Kenley 2014), and FDA identified no additional articles in the literature assessing the toxicological profile of AOD-9604.

In the article published by Moré and Kenley (2014), the authors report the conduct of the following nonclinical repeat-dose toxicity studies with AOD-9604:

- Four-week IV toxicity study in male and female Sprague-Dawley rats [Doses: 0.1, 1.0 or 10 mg/kg/day; vehicle: L-glutamic acid/D-mannitol buffer; n = 10/sex/treatment group]. Rats were 7 to 8 weeks old at the start of treatment. Measured outcomes included: (i) clinical signs, (ii) body weight, (iii) food consumption, (iv) hematology, (v) blood biochemistry, (vi) urinalysis, (vii) ophthalmoscopy, (viii) anti-AOD-9604 antibodies, and (ix) macroscopic and microscopic evaluation of different organs.

- Six-month oral toxicity study in male and female Han Wistar rats [Doses: 0.5, 20 and 100 mg/kg/day; vehicle: polyethylene glycol-400 (PEG-400); n = 12/sex/treatment group]. Rats were 48 to 52 days old at start of treatment by oral gavage. Measured outcomes were the same as those in the four-week toxicity study.

- Nine-month oral toxicity study in male and female Cynomolgus monkeys [Doses: 0.5, 10 or 50 mg/kg/day; vehicle: PEG400; n = 7/sex/treatment group]. Monkeys were 26 to 51 months old at the start of treatment by oral gavage. Measured outcomes included: (i) clinical signs, (ii) body weight, (iii) hematology, (iv) blood biochemistry, (v) urinalysis, (vi) electrocardiogram, (vii) ophthalmoscopy, and (viii) macroscopic and microscopic evaluation of different organs.

In the article, the authors provide a qualitative and limited high-level description of the overall findings, which are summarized below. In short:

- In the 4-week IV toxicity study:
  - Mean body weight gain of female rats at the middle and high AOD-9604 doses (1.0 and 10.0 mg/kg/day) was significantly lower than that of control female rats from weeks 1 to 4.
  - Mean body weight gain of male rats treated with the high AOD-9604 dose (10.0 mg/kg/day) was lower than that of control rats from weeks 2 to 4; however, the reduction did not reach statistical significance.
  - No other test article-related effect is described.

Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (January 2010), available at https://www.fda.gov/media/71542/download.

[61] 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.

- In the 6-month oral toxicity study in rats:
  - There was a trend for lower mean body weight gain and lower food consumption among female rats treated with the low and middle AOD-9604 doses (0.5 and 20.0 mg/kg/day).
  - At treatment week 13 (but not 26), male rats treated with all AOD-9604 doses had significantly higher blood urea concentrations than control males.
  - At treatment weeks 13 and 26, male rats treated with the high AOD-9604 dose (100 mg/kg) had significantly higher blood creatinine and triglyceride levels than control male rats.
  - At treatment week 13, male rats treated with the high dose and female rats treated with the mid and high doses of AOD-9604 had significantly lower blood osteocalcin levels than control, sex-matched rats.
  - At treatment week 26, female rats in the mid- and high-dose groups had significantly higher osteocalcin levels than control female rats.

- In the 9-month oral toxicity study in monkeys:
  - There were no test article-related effects on body weight, ophthalmic, electrocardiographic, hematological, or urinalysis findings.
  - At the end of treatment, all test article-treated male (but not female) groups had statistically lower liver masses and lower liver glycogen levels compared to controls.
  - Minimal or slight periportal vacuolation was present in the liver of two males given the mid AOD-9604 dose (10 mg/kg/day) and in the liver of one control female, one female treated with the low AOD-9604 dose (0.5 mg/kg/day), and all females given the high AOD-9604 dose (50 mg/kg/day). The pathology narrative does not include a description of the potential contents of the vacuoles.

Overall, the authors concluded that their findings were of no toxicological relevance because of lack of dose-response relationships and/or absence of any corroborative pathology (Moré and Kenley 2014). However, this conclusion should be interpreted with caution because:

- The authors provided no data tables, graphs, or statistical data analyses and did not describe the magnitude of the changes they noted in the different repeat-dose toxicity studies.

- As described in the article and summarized above, the changes in serum osteocalcin levels in male and female rats treated with AOD-9604 for 6 months appeared to show a clear dose and time dependence. Osteocalcin is a bone-derived hormone normally secreted by osteoblasts in the bone marrow and the circulation. In humans, blood osteocalcin levels are generally increased in metabolic bone conditions associated with increased bone turnover (e.g., osteoporosis, osteomalacia, and hyperparathyroidism). Conversely, blood osteocalcin levels are generally decreased in diseases characterized by reduced bone turnover (e.g., hypoparathyroidism and Cushing's syndrome) (Kruse and Kracht 1986). Therefore, there is concern that AOD-9604-induced changes in serum osteocalcin levels in rats might represent negative effects of AOD-9604 on bone health.

AOD-9604-induced changes in serum osteocalcin levels can be interpreted as a clinically relevant nonclinical safety signal.

- As described in the article and summarized above, the incidence of periportal vacuolation in the liver of female monkeys at the end of their 9-month treatment with AOD-9604 also appeared to increase dose dependently, being detected in all female monkeys in the high-dose group. Since cytoplasmic vacuolation of hepatocytes can be a signal of drug-induced liver injury (Tamai et al., 2017), the possibility cannot be ruled out that AOD-9604-induced cytoplasmic vacuolation of hepatocytes may represent a clinically relevant nonclinical safety signal.

At the time of this evaluation, the nominator did not submit, and FDA did not identify repeat-dose toxicity studies of subcutaneously or transdermally delivered AOD-9604 (free base) or AOD-9604 acetate.

e. Genotoxicity[62]

In the article published by Moré and Kenley (2014), the authors report the conduct of in-vitro and in-vivo genotoxicity tests with AOD-9604. The paragraphs that follow discuss the qualitative summary of findings provided by the authors in the article. We note that the published article does not provide tables or figures with the data generated in the different experiments.

Findings from bacterial reverse mutation (AMES) assays are equivocal. In the assays, AOD-9604 (dissolved in DMSO) was tested at concentrations ≤ 2,000 µg/plate for its ability to induce mutations in four *Salmonella typhimurium* strains (TA1535, TA1537, TA98 and TA100) and one *Escherichia coli* strain (WP2 uvrA) in the presence and in the absence of metabolic activation with S9 (the source of S9 is not defined). According to the authors, AOD-9604 produced no mutagenic signal in a plate incorporation assay with or without S9. However, in a preincubation assay with S9, AOD-9604 at 200 µg/plate and 1,000 µg/plate increased the number of WP2 uvrA revertants. Since the mutagenic signal was not reproduced in a second preincubation assay, the authors interpreted the findings of the first experiment to be of no relevance. This interpretation should be taken with caution because: (i) the authors did not identify or discuss factors that could have accounted for the inconsistent findings between duplicate assays, and (ii) as discussed in the next paragraphs, inconsistent/inconclusive results were obtained from other genotoxicity tests.

A micronucleus assay was conducted in bone marrow harvested from rats treated with AOD-9604 (0.1, 1.0, or 10 mg/kg/day, IV) for 4 weeks and from rats treated with a single dose of the positive control cyclophosphamide (10 mg/kg, IV). The authors report that there was an increase in micronucleus formation in the bone marrow of rats treated with the low and high AOD-9604 doses. Because the authors did not observe a clear dose-response relationship, they concluded

[62] 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.

that the response could not be taken as evidence that AOD-9604 causes chromosomal damage. However, the author's conclusion should be interpreted with caution because: (i) quantitative assessment of the number of micronuclei in the bone marrow harvested from rats treated with the different doses of AOD-9604 or with the positive control is lacking in the article, and (ii) equivocal genotoxicity signals were identified in the in-vitro AMES assays described in the previous paragraph and the in-vitro chromosome aberration assays described in the next paragraph.

In-vitro chromosome aberration assays were conducted in cultured CHO cells harvested at 1.5 cell cycles or at 24 hours after a 3-hour incubation of the cultures with AOD-9604 (0, 20, 50, 100, or 200 µg/mL) in the presence and in the absence of S9. The authors report that, in one assay, AOD-9604 had no effect on the number of chromosome aberrations. However, in a duplicate assay, an increase in the number of chromosome aberrations was observed in cells that were harvested at 1.5 cell cycles after the 3-hour incubation with the AOD-9604 concentration of 100 µg/mL (without S-9). The authors considered the positive genotoxicity signal to be of no biological significance because at a higher concentration (200 µg/mL) AOD-9604 appeared to have no effect on the incidence of chromosome aberrations in CHO cells. However, we note that AOD-9604 precipitated at this higher concentration. Since it is unclear how much AOD-9604 remained in solution, the negative finding is uninterpretable.

In conclusion, in the absence of quantitative data assessments, findings of positive genotoxicity signals produced by AOD-9604 in different in-vitro and in-vivo assays cannot be regarded as biologically insignificant.

f. Developmental and reproductive toxicity[63]

At the time of this evaluation, the nominator did not submit, and FDA did not identify nonclinical developmental and reproductive studies of AOD-9604 (free base) or AOD-9604 salt.

g. Carcinogenicity[64]

At the time of this evaluation, the nominator did not submit, and FDA did not identify nonclinical carcinogenicity studies of AOD-9604 (free base) or AOD-9604 salt.

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[63] 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 2012), available at https://www.fda.gov/media/148475/download.

[64] 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.

Conclusions: At the time of this evaluation, the nominators submitted, and FDA identified a limited number of nonclinical pharmacological studies reporting that AOD-9604 (a fragment of the C-terminal domain of hGH): (i) reduces lipogenesis, increases lipolysis and fatty acid oxidation, and decreases body weight in obese rodents, (ii) has no effect on plasma glucose and insulin levels or on glucose oxidation in rodents, and (iii) improves knee joint healing in a rabbit model of knee osteoarthritis. There are reports that AOD-9604 does not bind to or activates hGH receptors, and findings from one study suggest that the lipolytic effects of AOD-9604 depend, at least in part, on β3 adrenergic receptor signaling. However, the molecular target(s) and the mechanism(s) of action underlying the pharmacological effects of AOD-9604 remain unknown, making it difficult to assess the biological plausibility of the pharmacological effects reported in the different studies.

At the time of this evaluation, there was one published article reporting the results of different nonclinical toxicological studies of AOD-9604. In a repeat-dose toxicity study conducted in rats treated orally with AOD-9604 for 26 weeks, there were dose-dependent changes in serum osteocalcin levels that could be suggestive of negative effects of AOD-9604 on bone health. Specifically, at treatment week 13, in male and female rats, AOD-9604 dose dependently decreased serum osteocalcin levels, a signal suggestive of increased bone turnover. At treatment week 26, in female rats, AOD-9604 dose dependently increased serum osteocalcin levels, a signal suggestive of reduced bone turnover. In a repeat-dose toxicity study conducted in Cynomolgus monkeys treated orally with AOD-9604 for 9 months, the presence of minimal or slight periportal vacuolation in hepatocytes could be an indication of AOD-9604-induced liver damage. These nonclinical findings suggest that clinically relevant safety signals may develop with systemic exposures to AOD-9604. However, at the time of this evaluation, FDA did not identify nonclinical pharmacokinetic, toxicokinetic, and toxicological studies to establish the degree of systemic exposures generated by and the toxicological profile of AOD-9604 (free base) and AOD-9604 acetate delivered via the nominated ROAs. Genotoxicity studies were inconclusive, as AOD-9604 induced equivocal mutagenic signals in in-vitro AMES tests, in-vitro chromosome aberration assays, and in-vivo micronucleus assays. In conclusion, at the time of this evaluation, nonclinical studies were too limited in scope to inform safety considerations for the potential clinical uses of AOD-9604 (free base) or AOD-9604 acetate delivered via the nominated ROAs.

2. Human Safety

The following databases were consulted in the preparation of this section: PubMed, Embase, FDA Adverse Event Reporting System (FAERS), the Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS), ClinicalTrials.gov, relevant professional healthcare organization websites, and online clinical references and websites e.g., NIH.

The clinical publications submitted by the nominators and those identified by FDA do not clearly identify whether the AOD-9604 form administered was a salt formulation or the free base. Therefore, throughout this section, the substance will be generally referred to as AOD-9604

unless the article under discussion clearly specified use of the free base or acetate salt.

a. Pharmacokinetic data

FDA did not identify clinical studies in humans assessing pharmacokinetics or pharmacodynamics of AOD-9604 via any ROA.

b. Reported adverse reactions (FAERS, CAERS (if applicable), and case reports and anecdotal cases assessing safety)

FAERS:
The Office of Surveillance and Epidemiology (OSE) conducted a search of the FAERS database and medical literature for reports of adverse events (AEs) associated with oral, subcutaneous injectable or transdermal AOD-9604 through January 7, 2024. The FAERS search did not retrieve any reports, and the literature search did not identify any literature cases of adverse events.

OSE added that the lack of reports for AOD-9604 does not imply that the substance is safe or lacks toxicities. It is important to note that FAERS data have limitations.[65] Considering these limitations, OSE cannot make definitive conclusions regarding the safety of AOD-9604.

CFSAN
CFSAN collects reports of AEs involving food, cosmetics, and dietary supplements in the CAERS. A search of CAERS was conducted for AEs associated with AOD-9604 for the date range of 1/1/04 to 4/3/24 and did not retrieve cases.

We did not find case reports on the use of AOD-9604 that include safety assessment.

c. Clinical studies assessing safety

Both nominators cited a reference (Stier et al. 2013) that provided safety information on IV and oral AOD-9604 in humans. The nomination did not include, and our search of the published medical literature did not identify human exposure to AOD-9604 administered via SC or transdermal ROA.

Stier et al. 2013[66]: In this reference, the authors presented a summary of the safety data of AOD-9604 obtained in six R, DB, PC clinical studies. Within all the clinical studies, subjects received either AOD-9604 (Metabolic Pharmaceuticals Ltd.) or placebo (vehicle of mix of excipients). Safety monitoring included interview of subjects for AEs, measurement of vital signs, laboratory

[65] It is important to note that FAERS data have limitations. In general, there is no certainty that reported adverse event was due to the suspect product. FDA does not require that a causal relationship between a product and event be proven, and the report may not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that may potentially occur with a product, especially for compounded products. Considering these limitations, FDA cannot make definitive conclusions regarding the safety of AOD-9604..For additional information, see https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers

[66] Per Stier et al. 2013 the authors are either employees or consultants of Metabolic Pharmaceuticals Pty Ltd (Australia) which funded the six trials.

parameters (hematology; biochemistry, urinalysis, lipid analysis), and ECG. In addition, glucose tolerance, anti-AOD-9604 antibodies in the blood (in selected patients who received oral AOD-9604), serum levels of IGF-1 were measured. Studies are summarized below.

Intravenous:

METAOD001: Dose escalation study in 15 males (BMI 24 to 30 kg/m^2 age not specified)[67]. Subjects received 3 single doses of IV AOD-9604 ranging 25 to 400 mcg/kg (doses received per subject were not specified) and placebo, each separated by a wash-out period. The authors stated, "…a dose of recombinant hGH (rhGH) (0.12 international units/kg) was administered IV as positive control" but no details were provided about this "control." One subject terminated the study due to personal reasons;14 subjects completed the study. There were no serious AEs (SAE) reported. The AEs reported were headache (6), fatigue (4), hypoglycemia unspecified (3), dizziness (3), nasopharyngitis (2), cough (2) and 1 each for lethargy, tonsillitis, abdominal pain unspecified, application site reaction unspecified, sore throat unspecified, injection site bruising, rhinitis seasonal, anorexia, injection site pain. It was not specified what treatment and dose subjects were taking for these reported AEs. Per authors, the AEs were equally distributed between the various concentrations of AOD-9604 and placebo treatment; the AE profile was similar for all treatments.

METAOD002: A study in 23 males with obesity (19 to 50 years old) who each received 4 single doses of IV AOD-9604 25, 50, and 100 mcg/kg or placebo, separated by a 7-day washout period. No SAEs were reported. A total 118 AEs were reported (complete list was not provided). Three reported AEs were severe in intensity: 1 report of "feeling of chest tightness" in the 50 mcg/kg AOD-9604 group deemed possibly related to the AOD-9604, and 2 in the placebo group with no additional details provided. The most common AE reported by 16 subjects was mild or moderate headache. Mild or moderate intensity euphoria (AOD-9604 5, placebo 0) were deemed possibly related to AOD-9604. Authors concluded that the administration of AOD-9604 as single IV doses was well tolerated in the concentration range between 25 mcg and 400 mcg/kg bodyweight, and that the safety profile of AOD-9604 was comparable in all treatment groups.

Oral:

METAOD0003: A study in 17 males with obesity (34-54 years old) received 3 increasing doses of AOD-9604 (9, 27 and 54 mg) or placebo, separated by a 2-week wash-out period. There were 2 reported SAEs for 54 mg AOD-9604; diarrhea was possibly related to study treatment and pneumonia was deemed unrelated to the study treatment per authors. There were 97 AEs reported by 17 subjects, the most common AEs were headache, diarrhea, flatulence, increased appetite, and nausea. Authors claim there was no observed AE trend between the AOD-9604 groups and placebo. No additional details were provided to quantify reported AEs.

METAOD004: A R, DB, PC study in 36 males with obesity (18 to 54 years old) received either 9, 27 or 54 mg AOD-9604 or placebo (9 per group) for 7 days. No SAEs were

[67] BMI 25 to 29.9 kg/m^2 is considered overweight and BMI ≥30 kg/m^2 is considered obese in adults per NIH National Heart, Lung, and Blood Institute, accessed 5/22/24, https://www.nhlbi.nih.gov/health/overweight-and-obesity

reported. A total of 36 subjects reported 207 AEs, but AEs were not listed or quantified. Authors stated that: (i) the AE profile was "comparable in the 9 mg, 27mg AOD-9604 and the placebo group," and (ii) "subjects who received 54 mg AOD-9604 experienced a greater number of headaches, diarrhea and flatulence." No additional details were provided.

METAOD005: A DB, PC study in 300 males and females with obesity (30 to 60 years old) received once daily dose of AOD-9604 (1, 5, 10, 20 or 30 mg) or placebo (50 per group) once daily-for 12 weeks (3 months) after a 2-week run-in period. SAEs were reported by 5 subjects: basal cell carcinoma, moderate lipoma and squamous cell carcinoma (AOD-9604 20 mg), breast cancer (AOD-9604 5 mg) and malignant melanoma (AOD-9604 10 mg). Per authors, the Principal Investigator considered none of the SAEs reported to be related to study medication and added that none of the cancer forms occurred in the highest dosage group (30 mg AOD-9604); "therefore, a dose effect can be excluded." Authors stated the distribution of AEs were similar in the AOD-9604 and placebo groups. No further details on the specific SAEs or AEs were provided. Per authors, anti-AOD-9604 antibody analysis was performed at baseline, after 4, 8, and 12 weeks of treatment, and no subjects developed antibodies against the peptide during the study.

METAOD006: An R, DB, PC study in 502 males and females with obesity (no ages specified) received daily doses of AOD-9604 (0.25, 0.5, or 1 mg) or placebo for 24 weeks (6 months) after a 4-week placebo run-in period. Authors state that the distribution of SAEs were similar among all groups. No additional details were provided such as specific SAEs reported or treatment and dose received. For the active treatment period, the most commonly reported AE terms from four organ systems were: nasopharyngitis, headache, back pain and diarrhea. Authors state that: (i) "no AEs that were deemed to be definitely related to the study treatment," and (ii) "the percentage of AEs that were deemed to be "probably" or "possibly" related to study treatment was similar among all treatment groups." Per authors, no anti-AOD-9604 antibodies were detected in the subset of patients selected for antibody assay.

In all studies, per authors, no "statistically significant differences" in IGF-1 levels among the treatment groups and placebo group were detected. Anti-AOD-9604 antibodies were not detected in the subset of patients selected for antibody assays. There were no "statistically significant" changes in laboratory parameters, ECG changes, or vital signs in any treatment group.

In summary, based on this reference, the most commonly reported AEs associated with the use of IV AOD-9604 were headache (possibly related to AOD-9604), fatigue, hypoglycemia unspecified and dizziness. AEs assessed as possibly related to AOD-9604 were feeling of chest tightness (severe intensity) and euphoria (mild to moderate intensity). We note that studies on IV AOD-9604 are limited to small number of subjects and short study durations. For oral AOD-9604 use, the headache, diarrhea and flatulence were most commonly reported and SAEs reported include diarrhea deemed possibly related to AOD-9604. SAEs also reported in subjects who received oral AOD-9604 for 12 weeks were various types of cancers (basal cell carcinoma, moderate lipoma and squamous cell carcinoma, breast cancer and malignant melanoma) which were considered by the study investigators to be not related to AOD-9604.

We note the limitations of the study summaries on IV and oral AOD-9604 include lack of sufficient details such as detailed description and breakdown of AEs and SAEs, intervention and outcome, and/or a short-term study duration. There were no details provided on the laboratory values. We have concerns about the reports of various cancers reported with the 12-week study of oral AOD-9604 administration; information is insufficient whether these various types of cancers were unrelated to AOD-9604.[68]

d. Other safety information

Immunogenicity and aggregation concerns

FDA has issued guidance regarding immunogenicity assessment for therapeutic protein products.[69] The guidance describes immunogenicity as the propensity of a therapeutic protein product to generate immune responses to itself and to related proteins including endogenous proteins or peptides, or to induce immunologically related adverse clinical events. Although this guidance addresses therapeutic protein products, the concerns about immunogenicity are also relevant to peptides (such as AOD-9604 (free base) and AOD-9604 acetate), which can similarly elicit an immunogenic response; this immunogenic response may be enhanced when peptides are given via SC ROA. In general, SC ROA is associated with increased immunogenicity compared to IV ROA.

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

In addition, compared to small molecule active pharmaceutical ingredients (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).

We have limited information on immunogenicity or aggregation of AOD-9604 (free base) or AOD-9604 acetate and based on what we know about AOD-9604 (free base) or AOD-9604 acetate, these concerns would seem to apply to these substances. AOD-9604 consists of 16

[68] We note that OSE made comments about Stier et al. 2013, OSE stated it is unable to identify a safety signal from the limited data from the clinical trials described in the reference because of the different study designs, patient populations, treatment durations, formulations, and lack of case details (e.g., baseline concomitant medications, comorbidities).

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

amino acids, FDA is concerned about the potential for immunogenicity due to the potential for aggregation as well as potential peptide-related impurities. FDA has identified limited safety-related information for proposed routes of administration; thus, we lack sufficient information to know whether a drug product containing AOD-9604 (free base) or AOD-9604 acetate would cause harm when administered to humans. Based on available information there are insufficient data to conclude that AOD-9604 (free base) or AOD-9604 acetate does not present the above risks.

e. 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 compounded drug products containing AOD-9604 related BDSs.[70] See section II.C.1.c. for a list of FDA-approved drug products indicated for use as adjunctive therapy for weight management in patients with obesity.

Conclusions: Based on available information for AOD-9604 (free base) and AOD-9604 acetate, we conclude that the use of AOD-9604 related bulk drug substances in compounding may raise safety concerns.

There is limited clinical safety information on the use of AOD-9604 (free base) and AOD-9604 acetate. We did not find pharmacokinetic/bioavailability information for any route of administration. FDA did not find information on the proposed subcutaneous and transdermal use of AOD-9604 (free base) or AOD-9604 acetate in humans. Based on available studies in humans who received AOD-9604 via the oral ROA, serious AEs reported include diarrhea, chest tightness, and various types of cancers. We note there was insufficient information provided in these reports to assess relatedness of these AEs to AOD-9604 (free base) or AOD-9604 acetate, particularly the various types of cancers. In clinical studies conducted in subjects who received AOD-9604 via the IV ROA, AEs reported as possibly related to AOD-9604 were feeling of chest tightness (severe intensity) and euphoria (mild to moderate intensity). Obesity 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 AOD-9604 (free base) or AOD-9604 acetate in patients with obesity. There is no information to assess the pharmacokinetic or pharmacodynamic effects of AOD-9604 (free base) or AOD-9604 acetate in humans.

AOD-9604 (free base) or AOD-9604 acetate is a peptide containing 16 amino acids and peptide sequences of this length have the potential to be immunogenic. The safety profile of compounded drug products containing AOD-9604 (free base) or AOD-9604 acetate can be negatively impacted by various factors that include 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. There is limited information to assess immunogenic safety risk for AOD-9604 (free base) or AOD-9604 acetate for the oral route of administration and there is no information to assess immunogenic

[70] 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.

safety risk for the SC and transdermal topical routes. The nominations did not include, and FDA did not identify, information about AOD-9604 (free base) or AOD-9604 acetate to suggest that the substances do not present these risks.

There are multiple currently available FDA-approved drug products indicated to treat obesity.

III. CONCLUSION AND RECOMMENDATION

We have balanced the criteria described in section II above to evaluate AOD-9604-related substances for the 503A Bulks List. After considering the information currently available, a balancing of the criteria ***weighs against*** both AOD-9604 (free base) and AOD-9604 acetate being placed on that list based on the following:

1. Conclusions on the physical and chemical characterization for each AOD-9604 -related BDS, AOD-9604 (free base) and AOD-9604 acetate, are included in subsections 1.1 and 1.2.

    1.1. AOD-9604 (free base) is a peptide containing 16 amino acids with a disulfide bond between two cysteines at position 7 and 14. The presence of this disulfide bridge can lead to degradation by reducing the disulfide bond and aggregate formation (Janvier et al. 2018a; Janvier et al. 2018b).

    AOD-9604 (free base) is considered to be not physically and chemically well characterized because certain critical characterization data specific to AOD-964 (free base), such as potential peptide impurities, were not found in publicly available scientific literature and the provided CoA. Specific tests for AOD-9604 (free base) are not available in the public domain as well as in the submitted CoA, such as tests for impurities, aggregates, microbial test, and bacterial endotoxin test. As discussed in Section II.D.2.d, FDA is concerned about the potential for immunogenicity of AOD-9604 (free base) when formulated in an injectable dosage form for SC administration due to the potential for aggregation as well as potential peptide-related impurities, as discussed in the impurities section. Injectable routes of administration may present a particular risk for immunogenicity. We also note that the stability, pharmacological activity, and immunogenic properties of peptides such as AOD-9604 (free base) are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

    1.2. In addition, the nominators proposed transdermal cream and/or oral capsule as anticipated pharmaceutical dosage forms, in which polymorphism of the BDS is a critical attribute to ensure the efficacy of the compounded/finished drug product. However, information regarding the polymorphism of AOD-9604 (free base) is not available in the nomination packages as well as from the literature search.AOD-9604 acetate is an acetic acid salt form of AOD-9604 (free base). AOD-9604 (free base) is a 16 amino acid peptide with a disulfide bond between two cysteines at position 7 and 14. The presence of this disulfide bridge can lead

to degradation by reducing the disulphide bond and aggregate formation (Janvier et al. 2018a; Janvier et al. 2018b).

AOD-9604 acetate is considered to be not physically and chemically well characterized because certain critical characterization data specific to AOD-964 (free base), such as potential peptide impurities, were not found in publicly available scientific literature and the provided CoAs. Specific tests for AOD-9604 acetate are not available in the public domain as well as in the submitted CoAs, such as tests for specific impurities, aggregates, and microbial test. As discussed in Section II.D.2.d, FDA is concerned about the potential for immunogenicity of AOD-9604 acetate when formulated in an injectable dosage form for SC administration due to the potential for aggregation as well as potential peptide-related impurities, as discussed in the impurities section. Injectable routes of administration may present a particular risk for immunogenicity. We also note that the stability, pharmacological activity, and immunogenic properties of peptides such as AOD-9604 acetate are highly sensitive to the manufacturing process and quality attributes of the compounded/finished drug product.

In addition, the nominators proposed transdermal cream and/or oral capsule as anticipated pharmaceutical dosage forms, in which polymorphism of the BDS is a critical attribute to ensure the efficacy of the compounded/finished drug product. However, information regarding the polymorphism of AOD-9604 acetate is not available in the nomination packages as well as in the literature.

2. AOD-9604 was first developed in the late 1990s. The length of time and extent to which AOD-9604 has been used in compounding is unclear, however, there is some evidence of the use of AOD-9604 in compounding human drug products. AOD-9604 has been studied for use in obesity. It is currently being marketed for use in osteoarthritis, osteoporosis, worn cartilage, bone damage, hypercholesteremia, diabetes, depression, anti-aging, skin care, boosting metabolism, and supporting weight loss. Based on OF reporting data, no products were compounded containing AOD-9604 or AOD-9604 acetate. Internet search results show that compounders have prepared AOD-9604 drug products in injectable and oral formulations. These formulations are being marketed by medical spas and wellness clinics.

3. Based on available data, there is a lack of evidence to support the effectiveness of AOD-9604 for the treatment of obesity for any route of administration (ROA). Clinical practice guidelines for health professionals do not mention AOD-9604 (free base) or AOD-9604 acetate for treatment of obesity. The available information is limited to short summaries of clinical studies on the administration of oral or intravenous AOD-9604 which lack sufficient details about methodology and results. In most of the studies we identified, AOD-9604 failed to show benefit when compared to placebo. Importantly, a study conducted by Metabolic Pharmaceuticals Ltd. in Australia enrolled 536 patients with obesity and did not find a significant difference in weight loss after 12 weeks (the primary endpoint) with oral AOD-6904 compared to placebo. The company terminated development of the drug for obesity because of the failure of the study.

The nomination did not include, and FDA did not find, information on products containing AOD-9604 (free base) or AOD-9604 acetate administered by the subcutaneous or transdermal ROA in humans. Obesity increases the risk for many serious diseases and health conditions, and there are multiple FDA-approved drug products for use in weight management in patients with obesity.

4. According to an initial assessment of the toxicological profile of AOD-9604, safety signals suggestive of negative effects on bone health were apparent in rats treated orally with the peptide for 13 weeks. In addition, signals that could be indicative of potential liver toxicity were observed in Cynomolgus monkeys treated orally with peptide for 9 months. AOD-9604 also induced equivocal mutagenic signals in in-vitro and in-vivo genotoxicity assays. Nonclinical studies were not identified to establish the degree of systemic exposures generated by AOD-9604 (free base) and AOD-9604 acetate delivered via the nominated ROAs. In conclusion, at the time of this evaluation, nonclinical studies were too limited in scope to inform safety considerations for the potential clinical uses of AOD-9604 (free base) or AOD-9604 acetate delivered via the nominated oral, SC, and transdermal routes of administration (ROA).

   We did not find pharmacokinetic/bioavailability information for any ROA. Although nonclinical studies suggest that AOD-9604 is orally bioavailable in pigs and is pharmacologically active when delivered orally to rats, the extent of the oral bioavailability of AOD-9604 is unclear even in animals.

   Based on available information for AOD-9604 (free base) and AOD-9604 acetate, we conclude that the use of AOD-9604 related bulk drug substances in compounding may raise safety concerns.

   There is limited clinical safety information on the use of AOD-9604 (free base) or AOD-9604 acetate. FDA did not find information on the proposed subcutaneous and transdermal use of AOD-9604 (free base) or AOD-9604 acetate in humans. Based on available studies in humans, who received AOD-9604 via oral ROA, serious adverse events (AEs) reported include diarrhea, chest tightness, and various types of cancers. In clinical studies conducted in subjects who received AOD-9604 via the intravenous ROA, AEs reported as possibly related to AOD-9604 were feeling of chest tightness (severe intensity) and euphoria (mild to moderate intensity).

   Obesity 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 AOD-9604 (free base) or AOD-9604 acetate in patients with obesity. There is no information to assess the pharmacokinetic or pharmacodynamic effects of AOD-9604 (free base) or AOD-9604 acetate in humans. AOD-9604 (free base) or AOD-9604 acetate is a peptide containing 16 amino acids and peptide sequences of this length have the potential to be immunogenic. The safety profile of compounded drug products containing AOD-9604 (free base) or AOD-9604 acetate can be negatively impacted by various factors that include 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. There is limited information to assess immunogenic safety risk for AOD-9604 (free base) or AOD-9604 acetate for the oral ROA there is no information to assess immunogenic safety risk for the subcutaneous and transdermal topical routes. The nomination did not include, and FDA did not identify, information about AOD-9604 (free base) or AOD-9604 acetate to suggest that the substances do not present these risks.

There are multiple currently available FDA-approved drug products indicated to treat obesity.

On balance, physicochemical characterization, information on historical use, lack of evidence of effectiveness, and safety information for both AOD-9604 (free base) and AOD-9604 acetate weigh against them being added to the 503A Bulks List. Although available data suggests that these substances have historically been used in compounding, FDA's proposal is based on the lack of data related to physicochemical characterization, lack of evidence of effectiveness for use in obesity, and insufficient safety information on the use of the substances. These substances are not well characterized from a physical and chemical characterization perspective, and endotoxin testing for injectable route of administration (ROAs) is lacking. FDA also did not identify information that addresses additional concerns related to potential immunogenicity risk for AOD-9604 (free base) or AOD-9604 acetate, as described above. In most of the studies reviewed in this evaluation, AOD-9604 failed to show benefit for weight reduction when compared to placebo. Available clinical information indicates potential safety issues raised by the use of AOD-9604 related BDSs, such as diarrhea, chest tightness, euphoria, and various types of cancers. The lack of evidence of effectiveness and limited safety data discussed above and the existence of FDA-approved drugs for use in obesity, particularly in light of the fact that obesity increases the risk for many serious diseases and health conditions such as type 2 diabetes, heart disease, stroke, and certain types of cancers, weigh against AOD-9604-related bulk drug substance being added to the 503A Bulks List. Accordingly, we propose not adding AOD-9604 acetate or AOD-9604 (free base) to the 503A Bulks List.

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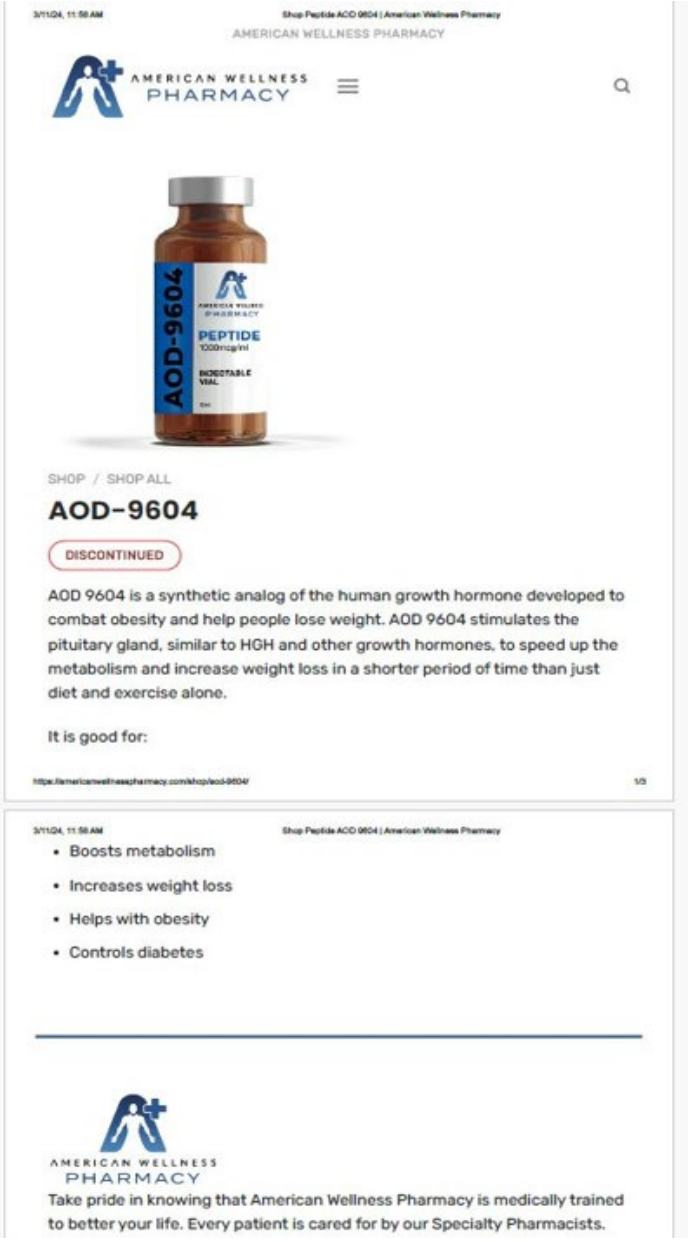
V. APPENDIX

APPENDIX 1: AMERICAN WELLNESS PHARMACY WEBPAGE (ACCESSED 3/11/24)



3/11/24, 11:58 AM Shop Peptide AOD 9604 | American Wellness Pharmacy

AMERICAN WELLNESS PHARMACY

AMERICAN WELLNESS PHARMACY

SHOP / SHOP ALL

AOD-9604

DISCONTINUED

AOD 9604 is a synthetic analog of the human growth hormone developed to combat obesity and help people lose weight. AOD 9604 stimulates the pituitary gland, similar to HGH and other growth hormones, to speed up the metabolism and increase weight loss in a shorter period of time than just diet and exercise alone.

It is good for:

https://americanwellnesspharmacy.com/shop/aod-9604/ 1/3

3/11/24, 11:58 AM Shop Peptide AOD 9604 | American Wellness Pharmacy

- Boosts metabolism
- Increases weight loss
- Helps with obesity
- Controls diabetes

AMERICAN WELLNESS PHARMACY

Take pride in knowing that American Wellness Pharmacy is medically trained to better your life. Every patient is cared for by our Specialty Pharmacists.

APPENDIX 2: REGEN DOCTORS WEBPAGE (ACCESSED 5/30/24)

AOD–9604 ACETATE

250 MCG RAPID ODT 30 MELTS 1 DAILY

$300.00

AOD stands for anti-obesity drug. AOD-9604 was originally developed to be used as an anti-obesity drug, and is known to help burn fat and support weight loss. AOD-9604 is a modified fragment of human growth hormone (HGH). AOD-9604 injection therapy can be prescribed to help stimulate the pituitary gland (similarly to HGH and other growth hormones) to boost metabolism, and support weight loss.

APPENDIX 3: LOW COUNTRY MALE WEBPAGE (ACCESSED 3/11/24)

A Complete Guide to AOD 9604 Peptide Therapy

No matter what your goal is, peptide therapy can assist you in losing weight or optimizing the health of your mind and body. The benefits of AOD 9604 are numerous and it may be able to assist you with your weight loss efforts in order to contribute to your overall vitality and fitness. Additionally, this peptide can contribute to other aspects of your overall health and provide impressive results.

Learn more about AOD 9604 by continuing to read.

Top Benefits of AOD 9604

Suggested: The Complete Guide to Peptide Therapy for Weight Loss

In order to fully comprehend the benefits of AOD 9604, we must first understand what this peptide actually does. Initially, AOD-9604 was used as an anti-obesity drug as it is a fragment of the growth hormone-releasing peptide (GHRP). By stimulating the pituitary gland, it helps the body regulate fat metabolism and reduce body fat.

AOD-9604 stimulates lipolysis, or the breakdown of fat, and inhibits lipogenesis. In addition, the amino acids contained in AOD 9604 are identical to those found in naturally

occurring growth hormone (hGH). In this process, nonfat food materials are converted into body fat. Paired with proper diet and exercise, peptide therapy can target abnormally high fat levels in the body.

The ability of AOD 9604 to regulate blood sugar levels and manage insulin levels is one of its most notable benefits. Consequently, inflammation will be reduced and weight loss will be achieved. AOD 9604 is also capable of enhancing the building of muscle, similar to growth hormone. It is well-established that the benefits of AOD 9604 extend beyond fat loss. It is known to contain a variety of regenerative properties, which may benefit individuals with a variety of conditions, including:

- Depression
- Diabetes
- Worn or damaged cartilage
- Bone damage

Additionally individuals with the following disorders may also benefit from AOD 9604:

- Osteoarthritis
- Osteoporosis
- Hypercholesterolemia

Related: The Ultimate Guide to Biohacking for Men

Administration and Dosage

An AOD 9604 treatment plan typically consists of two administration methods: orally or subcutaneously. Either way you choose, simply inject the AOD peptide about 30 minutes prior to eating in order to allow the peptide to fully metabolize and achieve optimal results.

A single injection in the morning is usually sufficient, but you may opt for multiple injections per day depending on your consultation. Ensure that you follow the dosage instructions provided by your healthcare provider.

Considerations

AOD-9604-Related Bulk Drug Substances (AOD-9604 (free base) and AOD-9604 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	AOD-9604
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	L-tyrosyl-L-leucyl-L-arginyl-L-isoleucyl-L-valyl-L-glutaminyl-L-cysteinyl-L-arginyl-L-seryl-L-valyl-L-alpha-glutamyl-glycyl-L-seryl-L-cysteinyl-glycyl-L-phenylalanine (7->14)-disulfide
Common Name(s)	AOD 9604, AOD9604, somatostatin (177-191), Tyr-, Tyr-somatostatin (177-191),
UNII Code	N/A
Chemical Grade	Provided by FDA Registered Supplier/COA
Strength, Quality, Stability, and Purity	Assay, Description, Solubility, etc.; Example of Attix Pharmacueticals Certificate of Analysis for this chemical is attached.
How supplied	Lyophilized Powder
Recognition in foreign pharmcopeias or registered in other countries	USA GRAS Status http://www.aspecthuntley.com.au/asxdata/20120625/pdf/01308164.pdf
Submitted to USP for monograph consideration	Yes
Compounded Dosage Forms	Subcutaneous Injectable, Transdermal Cream, Oral Capsule
Compounded Strengths	1,200 mcg/ml, 600 mcg
Anticipated Routes of Administration	Subcutaneous Injection, Transdermal cream, oral capsule
Saftey & Efficacy Data	Heffernan, MA, et al. (2001). Increase of fat oxidation and weight loss in obese mice caused by chronic treatment with human growth hormone or a modified C-terminal fragment. International Journal of Obesity (2001) 25, 1442–1449. DOI: 10.1038/sj.ijo.0801740
	Heffernan, M. (2001). The Effects of Human GH and Its Lipolytic Fragment (AOD9604) on Lipid Metabolism Following Chronic Treatment in Obese Mice and 3-AR Knock-Out Mice. Endocrinology, 142(12), 5182–5189. doi:10.1210/en.142.12.5182
	Khan, A., Raza, S., Khan, Y., Aksoy, T., Khan, M., Weinberger, Y., & Goldman, J. (2012). Current Updates in the Medical Management of Obesity. Recent Patents on Endocrine, Metabolic & Immune Drug Discovery, 6(2), 117–128. doi:10.2174/187221412800604644
	Kwon, D. R., & Park, G. Y. Effect of Intra-articular Injection of AOD9604 with or without Hyaluronic Acid in Rabbit Osteoarthritis Model. Annals of Clinical & Laboratory Science. (2015). 45(4), 426-432. doi: 0091-7370/15/0400-426.
	Berry, C. (2018). Bone, joint, and connective tissue disorders. Oxford Medicine Online. doi:10.1093/med/9780198719410.003.0009_update_001
	Mayer, M., Hocht, C., Puyo, A., & Taira, C. (2009). Recent Advances in Obesity Pharmacotherapy. Current Clinical Pharmacology, 4(1), 53–61. doi:10.2174/157488409787236128.
	Moré, M., Kenley, D. (2001). Safety and Metabolism of AOD9604, a Novel Nutraceutical Ingredient for Improved Metabolic Health. Journal of Endocrinology and Metabolism. 4(3), 64-77). doi:10.14740/jem213w.

	Stier, H et al. (2013). Safety and Tolerability of the Hexadecapeptide AOD9604 in Humans. Journal of Endocrinology and Metabolism. 3(1-2),7-15 doi:10.4021/jem157w
Used Previously to compound drug products	Yes
Proposed use	Osteoarthritits, Weight loss, Osteoporosis
Reason for use over and FDA-approved product	no FDA-approved product available
Other relevant information - Stability information	Added as an attachment

Attix Pharmaceuticals

APPROVED 6/2/17

Certificate of Analysis

AOD9604

Product Name : AOD9604
MW : 1815.1
Mfg. Date : Dec 03, 2016
CAS Number : 221231-10-3

Batch No. : A3629A
Formula: $C_{78}H_{123}N_{23}O_{23}S_2$
Exp. Date : Nov 30, 2019
Batch Qty: 3 g

Sequence: H-Tyr-Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe-OH

TESTS (Method Reference)	SPECIFICATIONS	RESULTS
Appearance (CP-9604)	White Powder	White Powder
Solubility (CP-9604)	2 mg should in 1ml water	Conforms
Identification by MS (CP-9604)	1815.1 ± 1	1814.4
Peptide Purity (CP-9604)	≥ 95.0%	99.80%
Water Content (Karl Fischer) (CP-9604)	≤ 8.0%	3.8%
Assay (CP-9604)	95.0% to 105.0%	98.0%
Conclusion: The product meets the specifications. Long Term Storage: Store in tight vials and Store in freezer.		

Note: Analytical results transcribed from the original COA provided by Chengdu KeJie Biopharm Co., Ltd, No. 137, Jiazidongdao, Dayi County, Chengdu, Sichuan, China. Lot Number: 20161203. COA available on Request.

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

	Name	Title	Signature	Date
Prepared by	Vidyenand Persaud	Operations Coordinator		05/23/17
Approved by	Syveon Liu	Lead Chemist		May 23/17

481 University Avenue, Unit 502, Toronto, Ontario M5G 2E9, Canada; Tel: (416) 594-1881; Fax: (416) 594-3737
www.attixpharmaceuticals.com

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?	AOD-9604
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in 207.3 (a)(4)? *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.	YES
Is the ingredient listed in any of the three sections of the Orange Book?	NO
Were any drug monographs for the ingredient found in the USP or NF monographs?	NO
What is the chemical name of the substance?	IUPAC Name: L-tyrosyl-L-leucyl-L-arginyl-L-isoleucyl-L-valyl-L-glutaminyl-L-cysteinyl-L-arginyl-L-seryl-L-valyl-L-alpha-glutamyl-glycyl-L-seryl-L-cysteinyl-glycyl-L-phenylalanine (7->14)-disulfide IUPAC Condensed: H-Tyr-Leu-Arg-Ile-Val-Gln-Cys(1)-Arg-Ser-Val-Glu-Gly-Ser-Cys(1)-Gly-Phe-OH $C_{78}H_{123}N_{23}O_{23}S_2$
What is the common name of the substance?	AOD 9604, AOD9604, somatostatin (177-191), Tyr-, Tyr-somatostatin (177-191) UNII: 7UP768IP4M 221231-10-3 AOD9604 AOD 9604
Does the substance have a UNII code?	7UP768IP4M
What is the chemical grade of the substance?	Provided by FDA Registered Supplier/COA

What is the strength, quality, stability, and purity of the ingredient?	Assay, Description, Solubility, etc.; Example of Certificate of Analysis for this chemical is attached.
How is the ingredient supplied?	Lyophilized Powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	USA GRAS Status http://www.aspecthuntley.com.au/asxdata/20120625/pdf/01308164.pdf
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?	Subcutaneous Injectable Transdermal Cream
What strength(s) will be compounded from the nominated substance?	1,200 mcg/mL 600 mcg/gm
What is the anticipated route(s) of administration of the compounded drug product(s)?	Subcutaneous Injection Transdermal Topical Cream
Are there safety and efficacy data on compounded drugs using the nominated substance?	Heffernan MA, Thorburn AW, Fam B, et al. Increase of fat oxidation and weight loss in obese mice caused by chronic treatment with human growth hormone or a modified C-terminal fragment. *Int J Obes Relat Metab Disord*. 2001;25(10):1442-1449. doi:10.1038/sj.ijo.0801740 Heffernan M, Summers RJ, Thorburn A, et al. The effects of human GH and its lipolytic fragment (AOD9604) on lipid metabolism following chronic treatment in obese mice and beta(3)-AR knock-out mice. *Endocrinology*. 2001 Dec;142(12):5182-5189. DOI: 10.1210/endo.142.12.8522. Stier H, Vos E, Kenley D. Safety and Tolerability of the Hexadecapeptide AOD9604 in Humans. *J Endocrinol Metab* 2013;3(1-2):7-15 doi:10.4021/jem157w Moré, M., Kenley, D. Safety and Metabolism of AOD9604, a Novel Nutraceutical Ingredient for Improved Metabolic Health. *J Endocrinol Metab*. 2014;4(3):64-77 doi:10.14740/jem213w Khan A, Raza S, Khan Y, et al. Current updates in the medical management of obesity. *Recent Pat Endocr Metab Immune Drug Discov*. 2012;6(2):117-128. doi:10.2174/187221412800604644 Kwon DR, Park GY. Effect of Intra-articular Injection of AOD9604 with or without Hyaluronic Acid in Rabbit Osteoarthritis Model. *Ann Clin Lab Sci*. 2015;45(4):426-432. Mayer MA, Höcht C, Puyó A, Taira CA. Recent advances in obesity pharmacotherapy. *Curr Clin Pharmacol*. 2009;4(1):53-61. doi:10.2174/157488409787236128

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?	Osteoarthritis, Weight loss, Osteoporosis
What is the reason for use of a compounded drug product rather than an FDA-approved product?	no FDA-approved product available
Is there any other relevant information?	Added as an Attachment

Certificate of Analysis

AOD9604 Acetate

Product Name	: AOD9604 Acetate	**Lot No.**	: DL5519
Mfg. Date	: Dec 01, 2019	**Exp. Date**	: Nov 30, 2022
M.F.	: $C_{78}H_{123}N_{23}O_{23}S_2$	**M.W.**	: 1815.1
CAS No.	: 221231-10-3	**Batch Qty**	: 275 g
Sequence	: H-Tyr-Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe-OH		

TESTS	SPECIFICATIONS	RESULTS
Appearance	White to off-white powder	White powder
Solubility	2mg should be soluble in 1mL of water	Conforms
Identification	1815.1±1	~~1814.4~~
Water Content (KF)	≤ 8.0%	3.8%
Peptide Purity (HPLC)	≥ 95.0%	99.8%
Acetate Content	≤ 15.0%	9.1%
Assay (anhydrous, acetic acid-free)	95 - 105%	99.2%
Conclusion: The product is a synthetic peptide and meets the specifications. Long Term Storage: Store in a sealed container at 2°C - 8°C in a Fridge ~~or Freezer~~. Distributed by Darmerica		

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

	Name	Title	Signature	Date
Prepared by	Sai Rasane	Quality Assistant		09/02/2020
Released by	Christina Boykin	Quality Assistant		09/04/2020

$(0.962)(0.909)(0.992) = 0.8675$

86.75%

9/29/2020

AOD-9604-Related Bulk Drug Substances (AOD-9604 (free base) and AOD-9604 acetate) Nomination Clarification

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?	AOD-9604
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in 207.3 (a)(4)? *Active ingredient* means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.	YES
Is the ingredient listed in any of the three sections of the Orange Book?	NO
Were any drug monographs for the ingredient found in the USP or NF monographs?	NO
What is the chemical name of the substance?	IUPAC Name: L-tyrosyl-L-leucyl-L-arginyl-L-isoleucyl-L-valyl-L-glutaminyl-L-cysteinyl-L-arginyl-L-seryl-L-valyl-L-alpha-glutamyl-glycyl-L-seryl-L-cysteinyl-glycyl-L-phenylalanine (7->14)-disulfide IUPAC Condensed: H-Tyr-Leu-Arg-Ile-Val-Gln-Cys(1)-Arg-Ser-Val-Glu-Gly-Ser-Cys(1)-Gly-Phe-OH $C_{78}H_{123}N_{23}O_{23}S_2$
What is the common name of the substance?	AOD 9604, AOD9604, somatostatin (177-191), Tyr-, Tyr-somatostatin (177-191) UNII: 7UP768IP4M 221231-10-3 AOD 9604 Acetate
Does the substance have a UNII code?	7UP768IP4M
What is the chemical grade of the substance?	Provided by FDA Registered Manufacturer & Supplier
What is the strength, quality, stability, and purity of the ingredient?	Purity (HPLC) 98.8%

How is the ingredient supplied?	Lyophilized Powder
Is the substance recognized in foreign pharmacopeias or registered in other countries?	USA GRAS Status http://www.aspecthuntley.com.au/asxdata/20120625/pdf/01308164.pdf
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?	Subcutaneous Injectable Transdermal Cream
What strength(s) will be compounded from the nominated substance?	1,200 mcg/mL 600 mcg/gm
What is the anticipated route(s) of administration of the compounded drug product(s)?	Subcutaneous Injection Transdermal Topical Cream
Are there safety and efficacy data on compounded drugs using the nominated substance?	Heffernan MA, Thorburn AW, Fam B, et al. Increase of fat oxidation and weight loss in obese mice caused by chronic treatment with human growth hormone or a modified C-terminal fragment. *Int J Obes Relat Metab Disord*. 2001;25(10):1442-1449. doi:10.1038/sj.ijo.0801740 Heffernan M, Summers RJ, Thorburn A, et al. The effects of human GH and its lipolytic fragment (AOD9604) on lipid metabolism following chronic treatment in obese mice and beta(3)-AR knock-out mice. *Endocrinology*. 2001 Dec;142(12):5182-5189. DOI: 10.1210/endo.142.12.8522. Stier H, Vos E, Kenley D. Safety and Tolerability of the Hexadecapeptide AOD9604 in Humans. *J Endocrinol Metab* 2013;3(1-2):7-15 doi:10.4021/jem157w Moré, M., Kenley, D. Safety and Metabolism of AOD9604, a Novel Nutraceutical Ingredient for Improved Metabolic Health. *J Endocrinol Metab*. 2014;4(3):64-77 doi:10.14740/jem213w Khan A, Raza S, Khan Y, et al. Current updates in the medical management of obesity. *Recent Pat Endocr Metab Immune Drug Discov*. 2012;6(2):117-128. doi:10.2174/187221412800604644 Kwon DR, Park GY. Effect of Intra-articular Injection of AOD9604 with or without Hyaluronic Acid in Rabbit Osteoarthritis Model. *Ann Clin Lab Sci*. 2015;45(4):426-432. Mayer MA, Höcht C, Puyó A, Taira CA. Recent advances in obesity pharmacotherapy. *Curr Clin Pharmacol*. 2009;4(1):53-61. doi:10.2174/157488409787236128
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?	Osteoarthritis, Weight loss, Osteoporosis
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?	The acetic acid (acetate) referenced on the C of A is a necessary by-product of chemical peptide manufacturing, as there must be a salt form produced during solid-phase peptide synthesis (i.e., salt exchange) to remove any toxic residues involved in peptide synthesis and manufacturing. It's not adding to or taking away any medicinal effect … and any salt content found in any peptide is factored out of the formulation concentration to provide a 100% pure peptide. 99.9% of all peptides are prepared via a process known as Solid Phase Peptide Synthesis (SPPS) and contain a required counter-ion component, most often it is acetic acid (resulting in an acetate molecule) and to a less frequent extent, sodium. These are by-products of the process that utilizes, most frequently, acetic acid or hydrochloric acid - used with a variety and series of cleavage cocktails used - in order to isolate the peptide from the polymeric support to remove toxic residuals/solvents/protecting groups required in the SPPS process of all peptides synthesized. The manufacturer could just as accurately provide the Product Name "AOD-9604", *sans acetate*. The CAS#, MF, and MW are all congruent with "AOD-9604". . If *any peptide* was received without a counter-ion exchange being performed, it would most likely be high in toxic residuals (such as Trifluoroacetic acid, TFA) from the cleavage cocktails used, and fail to meet standards. This is a primary reason NOT to purchase peptides via random internet sites, as they are not held or governed by any quality standards, nor are they regulated by any agency whatsoever, including the FDA; whereas compounding pharmacies are held to strict regulatory oversight by both the Boards of Pharmacy and the FDA by strict USP guidance. Lastly, once the peptide is prepared by the manufacturer, they must determine the correct product by Mass Spectrometry, the most used technique is a process called "*matrix-assisted laser desorption/ionization time-of-flight*" (MALDI-TOF). Synthetically prepared peptides tend to form salt adducts during the MALDI-TOF process. The most common salt adducts are sodium and potassium. This salt adduct does not affect the quality of the peptide and any residual sodium content that may be present (less than 2%) is factored out of the purity/potency of the product. Similar to Lidocaine Hydrochloride (Monohydrate) vs. Lidocaine, base. While a small salt conversion would be needed to attain equal "lidocaine" potencies, it is the same chemical, providing the same pharmacologic effect without any adverse "dangers". The attached C of A meets the definition of "bulk drug substance" in 207.3 (a)(4)

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CERTIFICATE OF ANALYSIS

Reference document : BPT-QC-STP-2001 V02

Product Name	AOD 9604 Acetate
CAS No.	221231-10-3
Molecular Formula	$C_{78}H_{123}N_{23}O_{23}S_2$
Lot No.	GIM120230510
Sequence	{Tyr}{Leu}{Arg}{Ile}{Val}{Gln}{Cys}{Arg}{Ser}{Val}{Glu}{Gly}{Ser}{Cys}{Gly}{Phe}
Modifications	Disulfide bridge:7-14
Storage Conditions	For less than 6-month storage, the recommended condition is 2-8℃; For longer term (> 6-month) storage, the recommended condition is minus 20℃.

Test Items		**Specifications**	**Results**	**Method**
Appearance		White to off-white powder	White to off-white powder (Conforms)	BPT-QC-SOP-2001 V02
Identification	**Molecular Weight (MS)**	1815.1±1.0Da	1814.9Da	BPT-QC-SOP-2001 V02
	Retention Time (HPLC)	The retention time of the major peak of the sample solution corresponds to that of the standard solution	Conforms	BPT-QC-SOP-2001 V02
Assay	**Purity (HPLC)**	≥98.0%	98.8%	BPT-QC-SOP-2001 V02
	Related Substances (HPLC)	Total Impurities(%)≤2.0% Largest Single Impurity(%)≤1.0%	1.2% 0.4%	BPT-QC-SOP-2001 V02
	Peptide Content (HPLC)	≥80.0%	86.0%	BPT-QC-SOP-2001 V02
Specific Tests	**Water Content (Karl Fischer)**	≤8.0%	7.6%	BPT-QC-SOP-2001 V02; USP<921>
	Residual Solvent (GC; HPLC)	Acetonitrile≤0.041% Trifluoroacetic≤0.500%	0.001% N.D	BPT-QC-SOP-2001 V02
	Bacterial Endotoxins (Gel-clot Method)	<10EU/mg	Conforms	BPT-QC-SOP-2001 V02; USP<85>
Conclusion	This batch was tested following the *analytical procedure of BPT-QC-SOP-2001 V02;* The test results met the *specifications of BPT-QC-STP-2001 V02*.			

Date of Mfg	10 May 2023	Date of Exp	09 May 2025
Date of Test	12 Jun 2023	Date of Release	12 Jun 2023
Quality Control: Yang Xu Yang Xu 12 Jun 2023 Reviewed		Quality Assurance: Yongna Zhao Yongna Zhao 12 Jun 2023 Approved	

Biopeptek Pharmaceuticals,LLC.

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Manufactured and Packaged at the FDA registered facility: 218 Shuangyuan Road, Chengyang, Qingdao, Shandong 266000, China (CHN)

The peptide is chemically synthesized

$(0.86)(0.988) = 0.8497$

84.97% ✓ 2nd MC 6/27/23

84.97%

06/27/2023

References included with nomination FDA-2015-N-3534-0467

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