FDA U.S. FOOD & DRUG ADMINISTRATION

October 2, 2026

Via Electronic Mail

[redacted]
Sr. Director-Global Regulatory Affairs-NA
Eli Lilly and Company
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Indianapolis, IN 46285

Re: *Eli Lilly and Co. v. Robert F. Kennedy, Jr. et al.* – Issues Remanded to FDA

Dear [redacted]:

Eli Lilly and Company (Lilly) submitted a request for designation (RFD) for retatrutide on January 19, 2024, that recommended that CDER regulate retatrutide as a biological product under a biologics license application (BLA).[1] On March 18, 2024, FDA responded to the RFD and stated that the Agency had determined that retatrutide is a drug, not a biological product. Specifically, FDA determined that retatrutide is neither a "protein" nor an "analogous product" to a protein, and therefore is not a biological product (see section 351(i)(1) of the Public Health Service (PHS) Act).

On September 3, 2024, Lilly filed a lawsuit against HHS and FDA in the United States District Court for the Southern District of Indiana challenging FDA's product classification determination and requesting that the Court require HHS and FDA to designate retatrutide as a biological product. In *Eli Lilly and Company v. Robert F. Kennedy, Jr. et al.*, 1:24-cv-01503, 2025 WL 2844524 (S.D. Ind. Oct. 3, 2025)), the Court remanded certain issues regarding the product classification of retatrutide to FDA for further consideration consistent with the Court's order. Specifically, the Court stated, in part: "remand is appropriate for the agency to identify, in a uniform fashion, the fundamental defining feature of 'analogous' proteins…. Once FDA decides, it must revisit its determination that retatrutide is not at least 'analogous' to a protein." The court commented that "there is a 'meaningful possibility that the agency could lawfully reach the same conclusion' if it determines the over-forty-[alpha amino acid] requirement is the critical defining feature of analogous proteins."[2]

The analysis below describes the basis for FDA's decision regarding the two critical characteristics of a "protein" that must be shared by an "analogous product" to a protein and the Agency's conclusion that retatrutide is not an analogous product to a protein and is therefore not a biological product. Accordingly, an application for retatrutide would need to be submitted under section 505 of the Federal

[1] This RFD was filed by FDA on January 23, 2024 ("Lilly RFD"). Lilly previously submitted an RFD for retatrutide on November 9, 2023; FDA issued a Not Filed Letter on November 17, 2023.

[2] *Lilly,* 2025 WL at *8.

Food, Drug, and Cosmetic Act.[3]

Background

On March 23, 2010, the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was enacted as part of the Patient Protection and Affordable Care Act (Public Law 111-148). The BPCI Act created an abbreviated licensure pathway for biological products that are biosimilar to or interchangeable with an FDA-licensed reference product. The BPCI Act also clarified the statutory authority under which certain products will be regulated by amending the definition of "biological product" in section 351(i) of the PHS Act by inserting the words "protein (except any chemically synthesized polypeptide)" before the words "or analogous product." On December 20, 2019, section 605 of the Further Consolidated Appropriations Act, 2020 (FCA Act) (Public Law 116-94), further amended the definition of a "biological product" in section 351(i) of the PHS Act by removing the parenthetical "(except any chemically synthesized polypeptide)"[4] from the statutory category of "protein."[5,6]

FDA has codified its interpretation of the statutory term "protein" in regulation.[7] FDA defined the term "protein" to mean "any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size. When two or more amino acid chains in an amino acid polymer are associated with each other in a manner that occurs in nature, the size of the amino acid polymer for purposes of

[3] FDA's Center for Drug Evaluation and Research will be responsible for the review of retatrutide, regardless of whether it is classified as a "drug" or a "biological product" (see "Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research" (June 30, 2003)).

[4] See also FDA Statement titled "Statement on low-cost biosimilar and interchangeable protein products," dated December 17, 2019, from Anna Abram, FDA Deputy Commissioner for Policy, Legislation, and International Affairs and Janet Woodcock, M.D., Director of FDA's Center for Drug Evaluation and Research (stating that "[r]emoving this exclusion will help patients because it provides the potential for chemically synthesized follow-on insulins and other protein products to come to market through more efficient abbreviated pathways, regardless of how they are manufactured").

[5] As amended by the BPCI Act and the FCA Act, a "biological product" is defined as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings" (see section 351(i)(1) of the PHS Act).

[6] FDA stated its contemporaneous understanding that "[t]his legislative change only affects chemically synthesized products that fall within the interpretation of 'protein'" and updated the "Preliminary List of Approved NDAs for Biological Products That Will Be Deemed to be BLAs on March 23, 2020 (current as of December 31, 2019)" on the FDA website to include the following three NDAs for chemically synthesized proteins that now fell within the statutory definition of a "biological product": NDA 020162 for Acthrel (corticorelin ovine triflutate), NDA 208471 for Adlyxin (lixisenatide), and NDA 022458 for Egrifta SV [and Egrifta] (tesamorelin acetate) (see https://www.fda.gov/drugs/guidance-compliance-regulatory-information/deemed-be-license-provision-bpci-act). In response to a comment to the public docket asserting that tesamorelin acetate is not a "protein" under FDA's definition (see FDA-2015-D-4750-0021), FDA explained in a March 20, 2020, memorandum to the file: "Specifically, we disagree with the assertion that tesamorelin acetate is not an alpha amino acid polymer because trans-3-hexonyl tyrosine is not an alpha amino acid. Even if the trans-3-hexonyl tyrosine, at one terminus of the tesamorelin acetate molecule, is not considered to be an alpha amino acid, the 43 other contiguous amino acids in the molecule are alpha amino acids. Therefore, tesamorelin acetate would still be a protein because it is an alpha amino acid polymer with a specific defined sequence of greater than 40 amino acids." The approved NDA for tesamorelin acetate (and the two other NDAs for chemically synthesized proteins) were deemed to be approved BLAs under section 351(a) of the PHS Act on March 23, 2020. As evidenced by the tesamorelin acetate example, FDA's consistent view has been that only alpha amino acids count for purposes of determining whether to classify a product as a protein, regardless of whether a product is naturally derived, chemically synthesized, or made using recombinant DNA technology.

[7] "Definition of the Term 'Biological Product,'" final rule (85 FR 10057, February 21, 2020). This rule became effective on March 23, 2020 ("Biological Product Definition Final Rule").

this paragraph (h)(6) will be based on the total number of amino acids in those chains, and will not be limited to the number of amino acids in a contiguous sequence" (21 CFR 600.3(h)).

Although FDA has codified its interpretation of a product "analogous" to other categories of "biological products" such as a virus, a therapeutic serum, and a toxin or antitoxin,[8] the Agency has not proposed a regulatory definition of an "analogous product" to a "protein." Instead, FDA has implemented the statutory category of an "analogous product" to a "protein" directly from the statute. In the preamble to the Biological Product Definition Final Rule, FDA stated, in response to a comment: "A definition of products that are 'analogous' to a 'protein' for purposes of section 351(i)(1) of the PHS Act is outside the scope of this rulemaking. We note, however, that it would not be appropriate for the statutory term 'analogous product' to be interpreted in a way that would include products that are specifically excluded by this final rule."[9]

As the current dispute concerning whether retatrutide is an "analogous product" to a protein illustrates, product classification questions are complex, drawing on the expertise of Agency scientists. Therefore, as discussed in the preamble to the final rule, despite the absence of a scientific consensus on certain aspects of the definition of "protein," FDA codified a "bright line" rule that encompasses alpha amino acid polymers that have characteristics that most scientists agree describe proteins, both to provide certainty for industry and to have a workable regulatory system.[10] If substances that lacked the critical characteristics of proteins could nonetheless be classified as "analogous products" to a protein, the "protein" definition would lose all utility because the Agency would have to undertake a resource-intensive analysis of the functional and structural characteristics of every substance offered for classification as an "analogous product" to a protein, even if it lacked the characteristics that FDA has determined are critical to considering a substance to be like a protein. This would create uncertainty and delay for innovator and follow-on product developers, which could in turn delay the availability of products to address important public health needs.

Based on FDA's evaluation of product classification requests to date, FDA considers the statutory category of an "analogous product" to a "protein" to apply in two scenarios. First, FDA developed factors to determine whether certain naturally derived mixtures are a "protein" or an "analogous product" to a protein to implement the transition provision of the BPCI Act.[11] For naturally derived mixtures that contain protein components (but are not known to be composed primarily of protein components) and also contain non-biological product components that can contribute to the product's activity, FDA determined that the naturally derived mixture is an "analogous product" to a protein if the

[8] See 21 CFR 600.3(h)(5); see also *Teva Pharms. USA, Inc. v. FDA*, 514 F. Supp. 3d 66, 69 (D.D.C. 2020) ("If anything, the diverse factors in the definitions suggest that "analogous product" takes on a meaning appropriate to each category it modifies, rather than a one-size-fits-all approach").

[9] 85 FR 10057 at 10061.

[10] 85 FR 10057 at 10059.

[11] See Memorandum dated March 18, 2020, from Biological Product Classification Subcommittee to (and signed by) Janet Woodcock, M.D., Director, CDER, Peter Marks, M.D., Ph.D., Director, CBER, and Thinh Nguyen, Director, OCP regarding "Recommendations on Factors for Determining Whether Certain Combination Products and Naturally Derived Mixtures Are Subject to the BPCI Act's Transition Provisions" (March 18, 2020, Memorandum). On March 23, 2020, an approved application for a biological product under section 505 of the FD&C Act was deemed to be a license for the biological product under section 351 of the PHS Act (see section 7002(e)(4)(A) of the BPCI Act; see also section 7002(e)(4)(B) of the BPCI Act). After March 23, 2020, all sponsors seeking approval of a biological product that previously could have been submitted under section 505 of the FD&C Act need to submit a marketing application under section 351 of the PHS Act.

identified protein component is necessary for the activity of the product and contributes to achieving the intended therapeutic effect.

Second, in the preamble to the Biological Product Definition Proposed Rule, FDA stated that "… for products with amino acid chains that are associated with each other in a manner that is not found in nature (*i.e.,* amino acid chains that are associated with each other in a novel manner that is not found in naturally occurring proteins), FDA would conduct a fact-specific, case-by-case analysis to determine whether the size of the amino acid polymer, for purposes of this definition, should be based on adding each of the amino acids in the amino acid chains together, or should be based on separate consideration of the amino acid chains (*e.g.,* the number of amino acids in the largest chain). In such cases, FDA would consider in its analysis, among other things, any structural or functional characteristics of the product."[12]

FDA further explained this approach when the Agency issued the Biological Product Definition Final Rule on February 21, 2020, and in response to a comment, stated:

> there are a number of ways in which amino acid chains could be associated with each other in a novel manner that is not found in naturally occurring proteins and we cannot predict all of these iterations. Although some of these combinations may result in amino acid polymers that exhibit characteristics generally associated with proteins, some may not. We recognize that the application of the fact-specific, case-by-case analysis for proposed products composed of amino acid chains that are associated with each other in a manner not found in nature does not provide the same level of certainty that is provided by the other criteria in § 600.3(h)(6) (see 83 FR 63817 at 63821), but it appears that case-by-case analysis is currently the best means of addressing such cases.[13]

The preamble discussion indicates that this analysis would be used to determine whether the active ingredient would be considered a "protein." However, the Agency's current view is that this fact-specific, case-by-case analysis is more appropriately conducted under the framework of an "analogous product" to a protein, given that an active ingredient that falls within this category is distinct from an active ingredient that meets the regulatory definition of "protein" because the alpha amino acid chains are associated with each other in a manner not found in nature.[14] Whether the fact-specific, case-by-case analysis is conducted under the framework for a "protein" or an "analogous product" to a protein does not affect the outcome of the classification decision.

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[12] Definition of the Term "Biological Product," proposed rule, (83 FR 63817 at 63821, Dec. 12, 2018) (Biological Product Definition Proposed Rule).

[13] 85 FR 10057 at 10060.

[14] FDA's revised thinking is consistent with the Agency's decision not to promulgate a definition of an "analogous product" to a protein at the time it did so for "protein," in order to give the Agency time to gain experience with this category of products. See March 18, 2020, Memorandum at 3, n. 7.

Analysis

I. FDA has identified two critical characteristics an active ingredient must have at a minimum, for it to be an "analogous product" to a protein.

FDA understands the statutory category of an "analogous product" to include a product containing an active ingredient that shares at least the critical characteristics of a "protein," but also is distinct from a protein in other ways such that it does not fall within the regulatory definition of "protein." As noted by the Court in *Teva Pharmaceuticals USA, Inc. et al. vs. FDA*, "[t]he 'analogous product' provision requires that some products not capable of identification as proteins be capable of identification as analogous products, and that the classification be based on some defining feature of proteins that analogous products share."[15]

Based on the Agency's scientific judgment, FDA has identified two critical characteristics that an active ingredient must have, at a minimum, to be considered an "analogous product" to a protein.[16,17]

A. Critical characteristic #1: The active ingredient contains one or more chains of alpha amino acids (where a "chain" of alpha amino acids refers to a contiguous sequence of alpha amino acids that are linked between the alpha-carboxyl group of one alpha amino acid and the alpha-amino group of the next alpha amino acid by a peptide bond)[18] that comprise an alpha amino acid polymer totaling greater than 40 alpha amino acids in size.[19]

A critical characteristic of a protein is the size of the alpha amino acid polymer because, despite the lack of a precise, agreed-upon definition of "protein," most sources agree that a "protein" refers to, among

[15] *Teva*, 514 F. Supp. 3d at 70; see also *Ipsen Biopharmaceuticals, Inc. v. Becerra*, 108 F.4th 836, 845-46 (D.C. Cir. 2024) ("By virtue of identifying analogous products, the FDA demonstrates that it is possible for an active ingredient to share a protein's critical characteristics, while also having other distinguishable characteristics").

[16] FDA acknowledges that it previously described a specific, defined sequence as "the" critical characteristic that an active ingredient must have in order for a product to be eligible to be an "analogous product" to a protein. *See Lilly*, 2025 WL at *7-8 (discussing Agency filing in *Teva*, 514 F. Supp. 3d 66). However, given that the active ingredient lacked that critical characteristic, there was not a need to identify another basis on which the active ingredient was ineligible to be an analogous product. Based on FDA's experience, FDA has determined that an active ingredient that lacks either critical characteristic identified above should not be classified as an "analogous product" to a protein, for the reasons set forth in this memorandum.

[17] See *Ipsen*, 108 F.4th at 844 ("the FDA contends that '[t]o be analogous to a category of biological products, a product must share the critical characteristics of the relevant category of biological product.' As to proteins, the FDA asserts that 'one such critical characteristic is the size of the amino acid polymer;' and 'a specific, defined sequence' is another") (internal citations omitted). Because the absence of a critical characteristic would inform the product classification decision, the Agency does not necessarily need to evaluate both critical characteristics for a particular substance.

[18] See Lodish, et al., Molecular Cell Biology (6th Ed. 2007) at 65 ("Individual amino acids are linked together in linear, unbranched chains by covalent amide bonds, called peptide bonds, with occasional disulfide bonds covalently linking side chains together. Peptide bond formation between the amino group of one amino acid and the carboxyl group of another results in the net release of a water molecule… The repeated amide N, α carbon (C_α), carbonyl C and oxygen atoms of each amino acid residue form the backbone of a protein molecule from which the various side-chain groups project…"); Alberts, et al., Molecular Biology of the Cell (4th ed. 2002) at 129 ("…there are 20 types of amino acids in proteins, each with different chemical properties. A protein molecule is made from a long chain of these amino acids, each linked to its neighbor through a covalent peptide bond").

[19] For purposes of this definition, we consider the associated chains of alpha amino acids to comprise a polymer.

other things, longer, more complex chains of alpha amino acids.[20] Without that property (and a specific, defined sequence, the other critical characteristic of a protein), an alpha amino acid polymer would not be "analogous" to a protein. As discussed above, an alpha amino acid polymer that is composed of 40 or fewer alpha amino acids is specifically excluded from the regulatory definition of "protein."

Where the size threshold for this critical characteristic is met by adding together the alpha amino acids in more than one "chain," the chains that can contribute to the total number of alpha amino acids are:

- chains that are associated with each other in a manner that occurs in nature; or
- chains that are associated with each other in a manner that does not occur in nature, where the association is necessary for the intended therapeutic effect and such effect would not be expected to occur without the association.[21] An association that modifies only pharmacokinetic parameters or duration of action, for example, generally would not be considered necessary for the intended therapeutic effect.

The A chain and B chain of insulin is an example of chains of alpha amino acids that are associated with each other in a manner that occurs in nature. To illustrate the criteria for the fact-specific, case-by-case analysis for chains that contribute to the total number of alpha amino acids when the chains are associated with each other in a manner that does not occur in nature, consider the hypothetical example of a chemically synthesized insulin in which the A chain and B chain are associated with each other in a manner that does not occur in nature. In this hypothetical example, the interaction between the A chain and B chain of insulin enables specific binding to the insulin receptor and subsequent downstream cellular signaling responses and thus is an association that is necessary to provide the intended therapeutic effect and such effect would not be expected to occur without the association. In contrast, the addition of a "side-chain consisting of glutamic acid and a C16 fatty acid" to an insulin analog would not be counted because it is not a contiguous sequence of alpha amino acids (plural) that are linked between the alpha-carboxyl group of one alpha amino acid and the alpha-amino group of the next alpha amino acid by a peptide bond. In addition, while the "side chain" alters pharmacokinetic parameters and extends the duration of action, consideration of structural and functional characteristics indicates that it is not necessary for the intended therapeutic effect.[22] As another example, an association between two chains of alpha amino acids (each of which contains 40 or fewer alpha amino acids) where each chain is intended to serve separate and independent functions would not fulfill this critical characteristic because the chains of alpha amino acids would not be associated with each other in a manner that is necessary to provide the intended therapeutic effect and such effect *would* be expected to occur without the association.

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[20] 83 FR 63817 at 63820.

[21] Note that, in response to the Court's remand order, this memo describes the analysis that FDA would undertake in evaluating alpha amino acid polymers with chains that are associated with each other in a manner that does not occur in nature. That analysis was not undertaken for retatrutide because, as discussed below, this analysis only is relevant only when there are two or more chains of alpha amino acids. FDA notes, however, that the isopeptide bond that occurs between the ADO moiety and the epsilon amino group of lysine residue 17 is a type of association that occurs in nature.

[22] See March 20, 2020, memo to file for NDA 208583 titled "Analysis of Xultophy 100/3.6 (insulin degludec and liraglutide injection) to determine whether NDA 208583 for this combination product is subject to the BPCI Act transition" (stating, in part: "Insulin degludec is composed of two amino acid chains consisting of 21 and 29 amino acids, respectively, that have specific, defined sequences and are associated with each other by two interchain disulfide bridges, which is a manner that occurs in nature.[8] Under FDA's interpretation of the statutory term 'protein,' the size of this amino acid polymer is based on the total number of amino acids in those chains, which is 50 amino acids. Therefore, insulin degludec is a 'protein' because it is an alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size." [The "side-chain consisting of glutamic acid and a C16 fatty acid" was not counted]).

The Agency's determination that only alpha amino acids are scientifically appropriate to consider for purposes of classification as a protein or an "analogous product" to a protein is consistent with the scientific consensus that the term "protein" refers to "amino acid polymers ('chains') made up of alpha amino acids linked by peptide bonds."[23] In an alpha amino acid, the amino group (NH_2) and the carboxyl (or carboxylic acid) group (COOH) are separated by a single carbon (C_α, the central alpha carbon). In a non-alpha amino acid, the amino group is not attached to the alpha carbon and may be separated from the carboxyl group by two or more carbon atoms and potentially other atoms as well. A non-alpha amino acid cannot form a peptide bond, which is defined as "[t]he covalent amide linkage between amino acid residues in a polypeptide chain, which is formed by linking the α-carboxyl carbon of one residue with the α-amino nitrogen of another."[24]

We only consider alpha amino acids to count toward the size threshold because only alpha amino acids can establish peptide bonds with one another, which results in "the net release of a water molecule" and allows the resulting amino acid residues to form a backbone of repeating amide N, alpha carbon (C_α), carbonyl C units (which refer to a CO group derived from the COOH group of an individual amino acid during peptide bond formation) that are essential to a protein's sequence.[25] The sequence (primary structure) of a protein determines its secondary and tertiary structure, which determines its associated function.[26] For that reason, scientists regard alpha amino acids as the "building blocks of proteins."[27,28]

B. **<u>Critical characteristic #2:</u>** The chain or associated chains of alpha amino acids have a specific, defined sequence.

Naturally occurring and recombinant proteins are made as a result of the synthesis of RNA from a DNA template (transcription) followed by translation into a protein molecule. For such proteins, the existence of a DNA template renders the sequence "specific and defined." Synthetic proteins may be generated by the stepwise addition of specific alpha amino acids or through other methods of chemical synthesis that result in a defined sequence of specific alpha amino acids. As one Court explained: "Put simply, as FDA reasonably concluded, molecules that do not have a specific, defined sequence are not

[23] 83 FR 63817 at 63820.

[24] See, e.g., Kendrew J, ed., The Encyclopedia of Molecular Biology (1994) at 806.

[25] See Lodish, et al., Molecular Cell Biology (6th Ed. 2007) at 65.

[26] See, e.g., Lodish, et al., Molecular Cell Biology 65-68 (6th Ed. 2007) (explaining how the sequence of alpha amino acids linked by peptide bonds determines a protein's primary, secondary, and tertiary structure); Berg JM, Tymoczko JL, and Stryer L, Biochemistry (10th ed. 2023), at 2.1.

[27] See, e.g., Berg JM, Tymoczko JL, and Stryer L, Biochemistry (10th ed. 2023), at 2.2 ("Amino acids are the building blocks of proteins. An α-amino acid consists of a central carbon atom, called the α carbon, linked to an amino group, a carboxylic acid group, a hydrogen atom, and a distinctive R group (also referred to as the side chain)"); Lehninger, Principles of Biochemistry (8th ed. 2021) at chapter 3 ("Cells produce proteins with strikingly different properties and activities by joining a common set of 20 amino acids in many different combinations and sequences. From these building blocks, different organisms can make such widely diverse products as enzymes, hormones, antibodies…").

[28] Proline has a secondary amine linked to both the alpha carbon and a side chain carbon in a ring structure, rather than the primary amine group linked to the alpha carbon in other alpha amino acids. Like other alpha amino acids, proline's "carboxyl" and "amine" groups are separated by a single "alpha carbon atom," so when a proline is incorporated into a protein chain it does not alter that chain's characteristic "backbone" structure (which consists of "a repeating sequence of three atoms corresponding to the amide nitrogen," the "central [alpha] carbon," and "the peptide carbonyl carbon"). See Creighton, Encyclopedia of Molecular Biology (1989) (entry for "polypeptide chain").

regarded as proteins in the scientific community, regardless of how they are made… Indeed, for FDA to find that chemically synthesized proteins need not share a characteristic that the agency, in reliance on scientific expertise, has identified as a defining trait of the category would deprive the term 'protein' of all set meaning."[29] For chemically synthesized proteins, an assessment of whether the chain or associated chains of alpha amino acids have a specific, defined sequence begins with the inquiry about whether there is a *chain* of alpha amino acids. A contiguous sequence of two or more alpha amino acids that are linked between the alpha-carboxyl group of one alpha amino acid and the alpha-amino group of the next alpha amino acid by a peptide bond is required to be considered a "chain" of alpha amino acids. A single alpha amino acid combined with other repeating chemical moieties may be a polymer, but it would not be considered an alpha amino acid polymer or a chain of alpha amino acids because it contains only one alpha amino acid.

In sum, to be an "analogous product" to a protein, an active ingredient must share these fundamental defining features of a protein, while also being distinct in other ways.

II. An "analogous product" to a protein is not required to be a "protein"—but an "analogous product" must share the two critical characteristics of a protein while being distinct from a protein in other ways.

FDA's interpretation of the term "analogous" does not require that a product have an active ingredient that is a protein in order for the product to be an "analogous product" to a protein.[30] FDA has found products with active ingredients that are not themselves proteins to be "analogous" to a protein. For instance, FDA considers a naturally derived mixture that contains multiple components to comprise a single active ingredient. FDA analyzed whether "naturally derived mixtures approved under an NDA that include one or more identified biological product component(s) (e.g., protein), as well as one or more non-biological product component(s) (e.g., lipids) that can contribute to the product's activity" should be deemed biological products.[31] These naturally derived mixtures *contain* a protein (i.e., the active ingredient includes an alpha amino acid polymer with a specific defined sequence that is greater than 40 alpha amino acids in size), but are not known to be composed primarily of protein components as their active ingredient (and are therefore not considered proteins), and also contain other types of molecules that contribute to their therapeutic effect. FDA determined that such naturally derived mixtures were "analogous" to a protein, and therefore should be regulated as biological products, "if the identified biological product (i.e., protein) component is necessary for the activity of the product and contributes to achieving the intended therapeutic effect." In other words, these active ingredients share the two critical characteristics of a protein, but do not meet the regulatory definition of a protein; FDA considers such naturally derived mixtures to be analogous products to a protein.

To illustrate, consider lung surfactants such as Infasurf (calfactant), which contains a protein (Surfactant Protein B (SP-B)), a peptide (Surfactant Protein C (SP-C)), and lipids (primarily phospholipids). The surfactant protein, SP-B, though present in relatively small quantities, is necessary for product activity and contributes to achieving the intended therapeutic effect through processing of SP-C precursor

[29] *Teva*, 514 F. Supp. 3d at 104 .

[30] FDA has stated that it will make case-by-case determinations that "leave[] open the possibility that other substances [it] has not considered and directly addressed could be analogous to a protein even if they are not themselves proteins" (see *Ipsen*, 108 F.4th at 846).

[31] See March 18, 2020, Memorandum.

protein, organization of surfactant phospholipids in lamellar bodies, formation of tubular myelin and generation of surfactant films.[32] Thus, such lung surfactants are regulated as biological products because they are "analogous products" to a protein.

In contrast, if a naturally derived mixture contained a protein as well as non-protein components, and the protein did not contribute to the product's intended therapeutic effect, the active ingredient would not be considered an "analogous product" to a protein and would be regulated as a drug product under the FD&C Act instead of a biological product under the PHS Act. For example, heparin is naturally derived from porcine mucosa and includes trace amounts of protein impurities. The presence of the protein impurities does not affect its classification as a drug product.

FDA does not agree that its approach to classifying these naturally derived mixtures effectively requires an active ingredient to *be* a protein in order to be classified as an "analogous product" to a protein. Indeed, the D.C. Circuit rejected a similar argument in *Ipsen*, characterizing the argument as "unfairly reductive." *Ipsen*, 108 F.4th at 846. As the *Ipsen* court explained, "quite simply, this mixture is a mixture. Some of the active ingredient's components are proteins, but others are not." *Id*. Further, the *Ipsen* court recognized that the kinds of mixtures FDA has found to be analogous to a protein show that "it is *possible* for an active ingredient to share a protein's critical characteristics[] while also having other distinguishable characteristics," *id.* at 845-46, and commented that FDA's approach to analyzing "analogous product" to a protein "leave[s] open the possibility that *other* substances that [it] has not considered and directly addressed could be analogous to a protein even if" they do not contain one. *Id.* at 846.

As another example of a product that could be an "analogous product" to a protein, consider a product containing an alpha amino acid polymer with a specific, defined sequence that is composed of two alpha amino acid chains, each of which has fewer than 40 alpha amino acids but which together total greater than 40 alpha amino acids. If the alpha amino acid chains do not associate with each other in a manner that occurs in nature, the alpha amino acid polymer would not fall within the definition of protein. Such a product containing the alpha amino acid polymer as its active ingredient could nonetheless be classified as an "analogous product" to a protein if FDA determines the associated chains have structural and functional characteristics that are "generally associated with proteins"[33] (e.g., the association is necessary for the intended therapeutic effect, rather than an association that modifies only pharmacokinetic parameters or the duration of action), and such effect would not be expected to occur without the association). While the Agency has not yet classified such a product, Agency expects it will review an increasing number of requests for classification of such products in the coming years.

III. Retatrutide is neither a "protein" nor an "analogous product" to a "protein" and thus is not a "biological product."

We have re-reviewed and carefully considered the information submitted by Lilly and available to the Agency, and we continue to disagree with Lilly's assertion that retatrutide is "analogous" to a protein.

In Lilly's RFD submission, Lilly asserted that "even if FDA concludes that retatrutide is not a protein . . .

[32] See March 20, 2020, memo to file for NDA 020521 titled "Analysis of Infasurf (calfactant) to determine whether NDA 020521 for this product is subject to the BPCI Act transition."

[33] *See Ipsen*, 108 F.4th at 846 (mentioning FDA's analysis of the structural and functional characteristics of Ipsen's product).

retatrutide nonetheless is analogous to a protein."[34] In the Agency's response to Lilly's RFD, we stated: "With regard to retatrutide specifically, as described above, being greater than 40 *alpha* amino acids is a fundamental, defining property of a protein, which retatrutide does not have. As a result, retatrutide cannot be analogous to a protein because it does not share this fundamental defining property. This same reasoning was upheld in *Teva Pharms. USA, Inc. v. FDA,* 514 F. Supp. 3d 66, 106 (D.D.C. 2020*)*, in which the court stated:

> FDA's stance, that a product cannot fail entirely to meet one of the agency's definitional criteria for a category of biological products yet nonetheless become a biological product, offers a reasonable method by which to distinguish sufficiently similar products from products that are too distinct to be considered analogous. The agency appears to understand the "analogous product" category as a narrow residual provision meant to accommodate products that satisfy the regulatory definitions of each category in most, if not all, regards, but are not an exact fit for whatever reason."[35]

FDA reaches the same conclusion that retatrutide is not an analogous product to a protein following the Agency's clarification of two critical characteristics of a "protein" that, in the Agency's scientific judgment, must be shared by an active ingredient that does not meet the definition of protein but is being evaluated to determine if it is an "analogous product" to a protein.

A. <u>Retatrutide does not contain one or more chains of alpha amino acids that total greater than 40 alpha amino acids in size</u>.

As discussed above, a critical characteristic that an active ingredient must have to be considered an analogous product to a protein is that it contains one or more chains of alpha amino acids that comprise an alpha amino acid polymer totaling greater than 40 alpha amino acids in size. Retatrutide does not share this critical characteristic because it does not contain one or more chains of alpha amino acids that total greater than 40 alpha amino acids in size.

Retatrutide is composed of a chain of 39 alpha amino acids and also contains a "side chain" composed of 8-amino-3,6-dioxaoctanoic acid (ADO) (identified with the red box above), gamma glutamate (identified

[34] Lilly RFD at 13.

[35] Letter from FDA Office of Combination Products to Lilly dated March 18, 2024, regarding request for designation ("RFD Response Letter") at 9; see also RFD Response Letter at 5 ("For purposes of this RFD response, we will assume, without deciding, that gamma glutamate is an alpha amino acid and that the associated chain composed of ADO and gamma glutamate is associated with the main 39-alpha amino acid chain in a manner that occurs in nature."). FDA's understanding of "analogous product" to a protein as a "narrow residual" category is consistent with Congress's intent to shift a discrete category of products from regulation under the FD&C Act to regulation under the PHS Act because the pathway for follow-on products created by the BPCIA is better suited to such products. See Memorandum from Director of FDA's Center for Drug Evaluation and Research and Director of FDA's Center for Biologics Evaluation and Research re: Interpreting the category "protein (except any chemically synthesized polypeptide)" in the revised definition of biological product, dated August 1, 2011, at 1-2.

with the blue box above), and a C20 fatty diacid moiety (identified with the green box above).[36] The ADO moiety on the "side chain" is linked to the epsilon amino group of lysine residue 17 on the 39-alpha-amino-acid chain via an isopeptide bond[37] and the ADO moiety also is linked to the gamma carboxyl group of the glutamate via an isopeptide bond (and therefore glutamate is described as "gamma glutamate").[38] The gamma glutamate is linked to a C20 fatty diacid moiety.[39] In the RFD Response Letter, we assumed without deciding that gamma glutamate is an alpha amino acid. However, we stated that "[e]ven if we assume that ADO is an amino acid, ADO is not an *alpha* amino acid because it does not contain an amino group and a carboxylic acid group separated by a single carbon, called the alpha carbon."[40] Accordingly, there is not an analysis in which retatrutide would be composed of greater than 40 alpha amino acids in size. However, for purposes of this response to Lilly's arguments, we considered on remand:

- Whether ADO is an amino acid;
- Whether gamma glutamate is an alpha amino acid; and
- Whether the 39-alpha amino acid chain associates with the ADO and gamma glutamate in a manner that occurs in nature.

1. ADO

An amino acid is defined as "[a]n organic compound containing at least one amino group and one carboxyl group."[41] ADO (8-amino-3,6-dioxaoctanoic acid) contains an amino group (-NH_2) at one end and a carboxylic acid group (-COOH) at the other end. Unlike an alpha amino acid (in which the amino group and carboxylic acid group are separated by a single carbon), the amino group and carboxyl acid group in ADO are separated by five carbon atoms as well as two oxygen atoms. Thus, ADO meets the chemistry definition of an amino acid. However, as explained in our RFD response, ADO does not meet the definition of an alpha amino acid because it does not contain an amino group and a carboxylic acid group separated by a single carbon.

FDA's conclusion regarding ADO in retatrutide is consistent with the Agency's treatment of ADO in tirzepatide, another Lilly product. Tirzepatide, approved by FDA in new drug applications (NDAs) 215866 and 217806 under the brand names Mounjaro and Zepbound, was identified by Lilly as a related product in its RFD because it is structurally similar to retatrutide in that it has a 39 alpha-amino-acid chain associated with "two ADO residues and one gamma-glutamate residue."[42] Lilly submitted an NDA for Mounjaro (tirzepatide) injection in September 2021, more than a year and a half after FDA finalized the

[36] RFD Response Letter at 5. The diagram is adapted from Lilly RFD at 1; however, FDA does not agree with the number "41" added by Lilly adjacent to gamma glutamate.

[37] An isopeptide bond is "an amide bond between a carboxyl group of one amino acid and an amino group of another amino acid, where either the carboxyl or amino groups or both are not α in position" (Lundblad, RL. Biochemistry and Molecular Biology Compendium (2019) at 175).

[38] RFD Response Letter at 2, note 4.

[39] RFD Response Letter at 2.

[40] RFD Response Letter at 5.

[41] Lodish, Molecular Cell Biology (6th ed.) at G-1 (which also states that "[i]n the amino acids that are the monomers for building proteins, an amino group and carboxyl group are linked to a central carbon atom, the α carbon, to which a variable side chain is attached.").

[42] Lilly RFD at 7-8.

regulatory definition of protein, and Mounjaro (tirzepatide) was approved in 2022.[43] In labeling dated July 28, 2023, Lilly described tirzepatide as "a 39-amino-acid … peptide" and referred to the "two ADO residues and one gamma-glutamate residue" as a "linker" that attached a C20 fatty diacid moiety (1,20-eicosanedioic acid) to the lysine residue on the 39-alpha-amino-acid chain.[44] At that time, Lilly did not describe tirzepatide as a 42-amino-acid protein based on the inclusion of ADO and gamma glutamate. It is only in its more recent labeling that Lilly omits the reference to a 39-amino-acid peptide.[45]

2. Gamma glutamate

Glutamic acid is an amino acid with a negatively charged side chain and is referred to as "glutamate" in its charged form.[46] Glutamate (represented by the letter E in the 39-alpha-amino-acid chain of retatrutide) contains an amino group and a carboxyl group separated by a single carbon (the alpha carbon) and is an alpha amino acid.[47] Gamma glutamate refers to a glutamate in which the second carboxyl group on the gamma carbon of the glutamate side chain (rather than the alpha carbon, which is two carbons away) participates in an isopeptide bond. In retatrutide, the carboxyl group on the gamma carbon of the glutamate side chain of gamma glutamate (identified with the blue box) forms an isopeptide bond with the amino group of the adjacent ADO (identified with the red box). Thus, gamma glutamate is considered an alpha amino acid because glutamate is an alpha amino acid; however, because glutamate is connected via an isopeptide bond (which is why it is described as "gamma glutamate") to a non-alpha-amino acid (ADO) in retatrutide, it does not participate in a chain of alpha amino acids.

3. Association of the 39-alpha amino acid chain with ADO and gamma glutamate

We do not need to reach the question of whether the 39-alpha-amino-acid chain is associated with ADO and gamma glutamate in a manner that occurs in nature because this analysis is relevant only when there are two or more chains of alpha amino acids. ADO and gamma glutamate do not comprise a chain of alpha amino acids—ADO is not an alpha amino acid and a single alpha amino acid cannot be a chain of alpha amino acids. Thus, the presence of gamma glutamate does not contribute to the total number of alpha amino acids.[48] Moreover, the relevant association would be between the 39-alpha amino acid chain and ADO (identified with the red box), which is not an alpha amino acid and may be described in this context as a linker.

For purposes of this response to Lilly's arguments, we note that the isopeptide bond that occurs between the ADO moiety and the epsilon amino group of lysine residue 17 is a type of association that

[43] See Mounjaro Approval Letter, www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/215866Orig1s000ltr.pdf.

[44] See 2023 Mounjaro Labeling, 11. Description available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215866Orig1s002s006lbl.pdf.

[45] See 2024 Mounjaro Labeling, 11. Description available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/215866s010s015s022lbl.pdf.

[46] Lodish, Molecular Cell Biology (6th ed.) at 42.

[47] See, e.g., Lodish, Molecular Cell Biology (6th ed.) at 42, Figure 2-14 ("The 20 common amino acids used to build proteins").

[48] We note that even if ADO and gamma glutamate were considered to be an alpha amino acid chain (which they are not) such that we counted gamma glutamate, the total number of alpha amino acids would only total 40, which is below the required threshold.

occurs in nature.[49] However, there would need to be an association between the 39-alpha amino acid chain and another chain of alpha amino acids—and ADO and gamma glutamate do not comprise a chain of alpha amino acids—to consider whether the number of alpha amino acids in the other chain contributes to the total number of alpha amino acids for purposes of 21 CFR 600.3(h)(6) and the assessment of an "analogous product" to a protein.

B. Retatrutide has a specific, defined sequence of 39 alpha amino acids.

Based on the information in Lilly's RFD submission, retatrutide is composed of a chain of 39 alpha amino acids and also contains a side chain composed of 8-amino-3,6-dioxaoctanoic acid (ADO), gamma glutamate, and a C20 fatty diacid moiety.[50,51] Lilly asserts that retatrutide has a specific, defined sequence "because it is synthesized according to 'a pre-defined template,' and it has an 'identical sequence across batches'" (citing *Teva*, 514 F. Supp. 3d at 106).

FDA considers the chain of 39 alpha amino acids to have a specific, defined sequence. In the regulatory definition of "protein," the alpha modifier in the term "alpha amino acid polymer" applies to the term "amino acid" in each aspect of the definition that follows. Accordingly, the "specific defined sequence that is greater than 40 amino acids in size" must be a specific defined sequence of more than 40 alpha amino acids. As discussed above, the "side chain" composed of ADO, gamma glutamate, and a C20 fatty diacid moiety is not a chain of alpha amino acids. Accordingly, the "side chain" is not relevant to the assessment of whether retatrutide has a specific, defined sequence for purposes of the regulatory definition. Rather, only the 39 alpha amino acids are relevant to the assessment of whether retatrutide has a specific defined sequence.

In summary, retatrutide does not have one of the two critical characteristics that, in the Agency's scientific judgment, must be shared by an active ingredient that does not meet the regulatory definition of a "protein" but is being evaluated to determine if it is an "analogous product" to a protein. Retatrutide is neither a "protein" nor an "analogous product" to a "protein" and is therefore not a biological product.

Finally, FDA does not agree with Lilly's argument that, as a result of the district court's decision in *Lilly*, 2025 WL 2844524 (S.D. Ind. Oct. 3, 2025), Lilly's recommendation that retatrutide be classified as a biological product should be considered FDA's final determination pursuant to 21 U.S.C. 360bbb-2(c). Product classification by operation of section 360bbb-2(c) is limited to the scenario in which is FDA fails to provide the written statement described in section 360bbb-2(b) in response to a request for designation within 60 days. Lilly's request for designation was submitted on January 19, 2024, and FDA responded on March 18, 2024, within the 60-day window. The statute simply does not address a scenario where the Agency responds but the response is later vacated by a court. FDA's understanding that the statutory deadline has no bearing on agency proceedings following judicial remand is consistent with how FDA and the courts have treated prior instances in which an Agency classification decision is

[49] For example, ubiquitin, a protein found in eukaryotic cells, binds to specific residues on a protein targeted for degradation via an isopeptide bond. See, e.g., Lodish, Molecular Cell Biology (6th ed.) at 88; Pickart CM. Mechanisms underlying ubiquitination. Annu Rev Biochem. 2001;70:503-33.

[50] RFD Response Letter at 5; see also RFD Response Letter at 2, note 4 (stating that the "ADO moiety is linked to the epsilon amino group of lysine residue 17 and to the gamma carboxyl group of the gamma glutamate via iso-peptide bonds").

[51] RFD Response Letter at 2.

vacated. See *Genus Med. Techs. LLC v. U.S. FDA*, 994 F.3d 631, 664 (D.C. Cir. 2021) (affirming a district court's vacatur of a request for designation while discussing various paths the agency might take on remand); *Prevor v. U.S. FDA*, 67 F. Supp. 3d 125, 139-40 (D.D.C. 2014) (similar). For these reasons, on remand, FDA has considered the question of whether retatrutide is an "analogous product" to a protein on the merits.

Sincerely,

JANICE L. WEINER -S

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