UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

ELI LILLY AND COMPANY,
Lilly Corporate Center
Indianapolis, IN 46285,

Plaintiff,

v.

XAVIER BECERRA, in his official capacity, and U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES,
200 Independence Avenue, S.W.
Washington, DC 20201,

and

ROBERT CALIFF, in his official capacity, and FOOD AND DRUG ADMINISTRATION,
10903 New Hampshire Avenue,
Silver Spring, MD 20993,

Defendants.

Case No. 1:24-cv-01503

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

INTRODUCTION

1. Retatrutide is an investigational product that, as an adjunct to a healthy diet and physical activity, offers the potential to help adults manage obesity and other, often chronic, health concerns such as sleep apnea, knee pain, and type 2 diabetes mellitus—conditions that afflict millions of Americans. Injected weekly, retatrutide works through a biological mode of action, targeting multiple receptors in the body to suppress appetite and increase energy expenditure.

2. Congress has given the Food and Drug Administration (FDA) authority in the Public Health Service Act (PHSA) to regulate "biological products"—including "proteins" and products "analogous" to proteins—that are "applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i)(1). But under the Supreme Court's recent *Loper Bright* decision, determining what falls within the statutory definition of "biological product" is an interpretative question that courts, rather than the agency, must ultimately resolve. *Loper Bright v. Raimondo*, 144 S. Ct. 2244, 2268 (2024); *see also id.* at 2296 (Kagan, J., dissenting) (identifying this specific question as one that courts must now resolve).

3. The agency's regulations define "protein" in relevant part by the number of amino acids it contains: a protein is "any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size." 21 C.F.R. § 600.3(h)(6). "[T]he size of the amino acid polymer" is "based on the total number of amino acids" in the polymer, so long as the chains are "associated with each other in a manner that occurs in nature." *Id.*

4. This case concerns FDA's determination that retatrutide, a product composed of 41 amino acids, is neither a protein nor analogous to a protein and is therefore not a biological product. FDA's decision contravenes both the governing statute and its own rules, and the Court should set it aside.

5. A product qualifies as a "protein"—and hence a biological product—under FDA's regulations if it: (1) is an "alpha amino acid polymer"; (2) has "a specific, defined sequence"; and (3) "is greater than 40 amino acids in size," counting "the total number of amino acids." *Id.* That aptly describes retatrutide, which is an alpha amino acid-containing polymer with a specific, defined sequence of 41 amino acids—40 alpha amino acids and one other, non-alpha amino acid—that are associated with one another in a manner that occurs in nature. On January 19, 2024, Plaintiff Eli Lilly and Company accordingly filed a request for designation asking FDA to classify retatrutide as a biological product.

6. On March 18, 2024, FDA rejected Lilly's request to designate retatrutide as a biological product and instead classified it as a drug. FDA did not dispute that retatrutide satisfies the first two requirements. But FDA determined that retatrutide does not satisfy the third requirement on the ground that it is not "greater than 40 amino acids in size." But 41 is plainly "greater than 40." FDA's decision, which is contrary to the PHSA and the agency's own regulations, is arbitrary, capricious, and not in accordance with law.

7. *First*, FDA's decision contravenes its own regulatory definition of "protein." Although the regulation states that a protein must be "greater than 40 amino acids in size," the agency now insists that it must be "greater than 40 *alpha* amino acids in size." But that limitation does not appear in the text, which distinguishes (including within the same sentence) between amino acids generally and the narrower category of alpha amino acids.

8. *Second*, FDA's determination that retatrutide is not a "biological product" is erroneous for an additional—and independent—reason. The PHSA defines the term to include, in addition to proteins, any product that is "analogous" to a protein. 42 U.S.C. § 262(i)(1). Retatrutide shares all critical characteristics with proteins composed solely of alpha amino acids: Its structure

and function are not meaningfully different than a protein composed solely of alpha amino acids. Even if retatrutide is not a protein, therefore, it still qualifies as a biological product because it is at least "analogous" to a protein.

9. FDA concluded that retatrutide is not "analogous" to a protein because it has fewer than 41 alpha amino acids and therefore does not satisfy the regulatory definition of "protein" (as the agency reads it). But that explanation—that retatrutide is not a protein so therefore cannot be analogous to a protein—contravenes the statute's plain language and collapses the statutory distinction between proteins and "analogous" products, effectively erasing an entire category of biological products from the PHSA. The agency's decision to limit "analogous" products to those that already satisfy its rigid "protein" definition is particularly suspect, given that the agency is not entitled to deference in interpreting either of those statutory terms.

10. FDA, like any agency, must act within statutory and regulatory constraints. It is bound to follow the statutory definition of "biological product" and the agency's own regulations interpreting the term "protein." This Court should set aside FDA's erroneous decision rejecting Lilly's proposed classification of retatrutide and should order the agency to properly designate retatrutide as a biological product.

JURISDICTION AND VENUE

11. This action arises under, and asserts violations of, the Administrative Procedure Act (APA), 5 U.S.C. § 551 *et seq.*, and the PHSA, 42 U.S.C. § 201 *et seq.* This Court has subject-matter jurisdiction under 28 U.S.C. §§ 1331, 1346, and 1361 and 5 U.S.C. §§ 701-06. An actual controversy exists between the parties within the meaning of 28 U.S.C. § 2201(a), and this Court may grant declaratory relief, injunctive relief, and other appropriate relief under 28 U.S.C. §§ 2201-02 and 5 U.S.C. §§ 705-06.

12. FDA's order denying a request to designate retatrutide as a biological product is a final agency action that is judicially reviewable under the APA. *See* 5 U.S.C. §§ 704, 706; *see also* 21 C.F.R. § 3.9(a).

13. Venue is proper in this Court under 28 U.S.C. § 1391(e) and 5 U.S.C. § 703 because this action seeks relief against federal agencies and officials acting in their official capacities; the plaintiff resides in this district; and a substantial part of the events or omissions giving rise to the claim occurred in this district.

PARTIES

14. Plaintiff Eli Lilly and Company is an Indiana corporation with a principal place of business in Indianapolis, Indiana.

15. Defendant Xavier Becerra is the Secretary of Health and Human Services and the head of the U.S. Department of Health and Human Services (HHS). He is responsible for administering and enforcing the PHSA, 42 U.S.C. § 201 *et seq*. He is being sued in his official capacity only. Secretary Becerra maintains an office at 200 Independence Avenue, S.W., Washington, DC 20201.

16. Defendant HHS is a Cabinet-level department of the United States government. Its headquarters are located in Washington, DC.

17. Defendant Robert Califf is the Commissioner of Food and Drugs and the head of FDA, an administrative agency within HHS. He is being sued in his official capacity only. Commissioner Califf maintains an office at 10903 New Hampshire Avenue, Silver Spring, MD 20993.

18. Defendant FDA is an administrative agency of the United States government within HHS. It is the division of HHS charged with administering the relevant statutory scheme. Its headquarters is located in Silver Spring, MD.

BACKGROUND

19. For more than a century, drugs and biological products have been regulated under separate but overlapping authorities. In order to clarify the law, Congress enacted the Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, Tit. VII, Subtit. A, 124 Stat. 804 (2010), which amended the PHSA to create a distinct pathway for approval of certain biological products. *See generally* Krista Hessler Carver et al., *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act 2009*, 65 Food & Drug L.J. 671, 681 (2010). As part of this legislation, Congress added the word "protein" to the statutory list of products that are "biological products" that are licensed under the PHSA. Pub. L. No. 111-148, § 7002(b)(2), 124 Stat. 814 (2010).

The PHSA Regulates "Protein[s]" and "Analogous Product[s]" as Biological Products

20. Under the PHSA, a person who introduces "any biological product" into interstate commerce must have a "biologics license." 42 U.S.C. § 262(a)(1). Congress has given the Secretary of HHS authority to oversee biologics licensing. *Id.* § 262. The Secretary relies on FDA to implement the licensing scheme.

21. An applicant must submit a biologics license application to obtain licensure of a "biological product," which Congress defined to include a "protein, or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." *Id.* § 262(i)(1). The statute does not further define "protein" or "analogous product," the meaning of which is accordingly an interpretive question for the courts. *See Loper Bright*, 144 S. Ct. at 2268;

see also id. at 2296, 2298, 2300 (Kagan, J., dissenting) (repeatedly identifying this question as one that courts now must resolve).

22. Under FDA regulations, "[a] protein is any *alpha amino acid polymer* with a *specific, defined sequence* that is *greater than 40 amino acids in size*." 21 C.F.R. § 600.3(h)(6) (emphases added). In adopting that definition, FDA acknowledged that there is no "clear scientific consensus" on the meaning of "protein," and the agency explained that it adopted its regulation in substantial part for policy reasons: to establish, for this one category of biological products enumerated in the statute, a "scientifically reasonable, bright-line rule that provides regulatory clarity and facilitates implementation" of the statute, as well as to "facilitate[] efficient use of time and resources both by FDA and applicants" and to "reduce[] regulatory uncertainty." 85 Fed. Reg. 10,057, 10,059 (Feb. 21, 2020).

23. **Alpha amino acid polymer**. FDA regulations do not define "alpha amino acid polymer"—nor, for that matter, "amino acid" or "alpha amino acid." Under generally accepted scientific principles, and under FDA practice, a "polymer" is a large molecule made up of smaller units or monomers, such as amino acids. An "amino acid" is a molecule that has both an amino group and a carboxylic acid group. And, according to an FDA "Memo to File," alpha amino acids are amino acids that "have the carboxyl group [of the carboxylic acid] linked to the alpha carbon of their carbon chain." FDA, Memo to File, *Teva Pharms. USA v. FDA*, Docket No. 1:20-cv-808 (D.D.C. 2020), Doc. 46, at FDA0292 n.3. An "alpha amino acid polymer," in the context of the agency's regulation and other guidance, is thus an alpha amino acid-containing polymer—that is, a large molecule (polymer) that includes at least some alpha amino acids.

24. **Specific, defined sequence**. For a product to have a "specific, defined sequence," its amino acids must be added to the polymer by "following a pre-defined template" that results in

an "identical sequence across batches." *Teva Pharms. USA, Inc. v. FDA*, 514 F. Supp. 3d 66, 106 (D.D.C. 2020).

25. **Greater than 40 amino acids in size**. To determine whether a product is sufficiently large, FDA regulations require counting all amino acids associated with one another in a naturally occurring manner:

> 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 . . . 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 C.F.R. § 600.3(h)(6) (emphasis added).

26. **Analogous product**. The PHSA defines "biological product" to include, in addition to proteins, any "analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i)(1). FDA regulations do not further define the term "analogous product" with respect to proteins.

The FDCA Authorizes a Request for Designation of a Product's Regulatory Classification—and Requires FDA to Respond within Sixty Days of Receipt

27. Section 563 of the Federal Food, Drug, and Cosmetic Act (FDCA) allows a person to "submit a request to the Secretary respecting the classification of [a] product," including a request that the product be classified as a drug or biological product. 21 U.S.C. § 360bbb-2(a).

28. FDA's regulations refer to this type of request as a "request for designation," sometimes called an RFD. 21 C.F.R. § 3.7.

29. Congress mandated that, "[n]ot later than 60 days after the receipt" of an RFD, the agency must "determine the classification of the product" and must issue a "written statement that identifies such classification." 21 U.S.C. § 360bbb-2(b).

30. If FDA "does not provide" a letter of designation by the 60-day statutory deadline, then "the recommendation made by the person" requesting classification "shall be considered to be a final determination" of the product's classification. *Id.* § 360bbb-2(c).

31. A final determination of a product's classification "may not be modified" except with the requester's "written consent," or else "for public health reasons based on scientific evidence." *Id.*

Lilly Develops Retatrutide to Treat Obesity, Diabetes, and Other Conditions

32. Obesity is a chronic disease that affects tens of millions of Americans. Obesity is associated with numerous other health conditions that shorten lifespans and diminish quality of life, such as sleep apnea, osteoarthritis in the knee, and type 2 diabetes mellitus.

33. Investing enormous resources and years of study, Lilly has developed retatrutide to help adults manage obesity and associated health concerns, including type 2 diabetes.

34. Retatrutide is an "agonist," meaning it targets specific receptors within the body. Injected into patients once a week, retatrutide binds to three different hormone receptors to reduce calorie intake and increase energy expenditure. This three-receptor (or tri-agonist) approach allows retatrutide, among other things, to stimulate substantial weight loss.

35. Lilly has subjected retatrutide to numerous tests to evaluate its safety and efficacy. These include animal studies, in vitro assays, and Phase 1 and Phase 2 clinical studies. In a 48-week, randomized, double-blind, placebo-controlled trial, use of retatrutide was associated with an average weight of reduction of 24.2%, along with significant improvements in cardiometabolic health (*e.g.*, blood pressure, LDL-cholesterol, fasting glucose, and insulin). Lilly is currently studying retatrutide further in Phase 3 clinical trials.

36. Retatrutide is a polymer containing alpha amino acids, composed of an amino acid backbone and an associated amino acid chain.

37. Retatrutide's backbone comprises a chain of 39 alpha amino acids linked together by peptide bonds. The backbone is connected to a second, associated chain composed of two more amino acids: gamma-glutamate, which is an alpha amino acid; and 8-amino-3,6-dioxaoctanoic acid (ADO), which is not. Both chains serve key functions. The chain of ADO and gamma-glutamate—along with an associated fatty acid—helps facilitate binding to albumin, thereby extending the molecule's pharmacokinetic half-life while simultaneously providing desired pharmacological properties.

38. ADO and gamma-glutamate are associated with optimal receptor activities, serum albumin binding, pharmacokinetics, and high solubility in a neutral pH formulation. The ADO also serves as a structural bridge when both the backbone and associated chain both bind to albumin, a typical function served by amino acids in a protein.

39. The backbone and associated chain are covalently bound to one another by an isopeptide bond, which is a type of bond found in naturally occurring proteins.

Lilly Requests Designation of Retatrutide as a Biological Product, and FDA Denies the Request

40. On November 9, 2023, Lilly submitted to FDA an RFD seeking designation of retatrutide as a biological product.

41. On November 17, FDA sent Lilly a letter stating that its RFD "ha[d] not been filed" because it did not contain sufficient information for the agency adequately to evaluate the request.

42. Lilly responded to FDA by letter on December 1. Among other things, Lilly explained that some of the information requested by FDA was irrelevant to Lilly's RFD, and other requested information could not be submitted without violating FDA's policy that RFDs "must not

exceed 15 pages, including attachments." 21 C.F.R. § 3.7(c). Lilly asked to meet with FDA to discuss the agency's concerns and how best to facilitate consideration of its RFD.

43. On December 15, representatives of FDA and Lilly met to discuss the RFD. In that conversation, FDA agreed that it did not need much of the information it had requested in its November 17 letter, and Lilly agreed to changes that would obviate or satisfy the agency's remaining requests. Lilly also agreed to submit a new RFD that would supersede the prior one.

44. On January 19, 2024, Lilly submitted a new RFD—which it identified as "supersed[ing]" the prior RFD—with the additional information requested by FDA.

45. On March 18, FDA issued a letter of designation denying Lilly's RFD. The agency "disagree[d] with [Lilly's] recommendation that retatrutide should be classified as a biological product" and instead "determined that [the] product is a drug."

46. According to FDA, retatrutide is not a protein because "it is not composed of more than 40 alpha amino acids." Although the agency did not dispute that retatrutide has 41 total amino acids, it took the position that "only alpha amino acids are relevant to determining whether something is a protein." The agency continued, "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." As a result, "ADO [wa]s not counted" toward the total, and thus in FDA's view retatrutide did not have "greater than 40 amino acids"—it just had 40. 21 C.F.R. § 600.3(h)(6).

47. FDA acknowledged that "the definition of protein in 21 C.F.R. § 600.3 does not repeat the 'alpha' modifier each time the definition uses the term amino acid," but the agency nevertheless asserted that "doing so was not necessary given that 'alpha amino acid polymer' was used at the beginning of the definition." The agency further asserted that its reading was supported

by "common scientific knowledge," a claim the agency supported with a footnote citing generally to a single source.

48. FDA "assume[d]" that the other components of the protein definition had been met: It "assume[d] (without conceding) that retatrutide has a specific defined sequence," "assume[d] that ADO is an amino acid," and "assume[d], 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." It did not include any contrary analysis.

49. FDA next concluded that retatrutide is not "analogous to a protein" because it does not satisfy "the bright line principle established by the rule"—that is, because retatrutide does not satisfy the definition of "protein" in 21 C.F.R. § 600.3(h)(6). According to the agency, treating retatrutide as "analogous" to a protein would "effectively include alpha amino acid polymers with fewer than 41 alpha amino acids within the scope of a rule that was intended to exclude them," thereby "defeat[ing] the purpose of the bright line rule because FDA would frequently have to evaluate on a case-by-case basis the features of a particular molecule to determine if it is analogous to a protein." The agency further stated, without citing any source, that "being greater than 40 *alpha* amino acids is a fundamental, defining property of a protein," such that "retatrutide cannot be analogous to a protein because it does not share this fundamental defining property."

50. In conclusion, FDA reiterated that the agency "disagree[d] with [Lilly's] recommendation that retatrutide should be classified as a biological product" and restated its view that retatrutide "is appropriately classified as a drug."

LEGAL ALLEGATIONS

51. Retatrutide is a "biological product" under the PHSA and under FDA's own regulations. FDA's denial of Lilly's request to designate retatrutide as a biological product is arbitrary, capricious, and not in accordance with law.

Retatrutide Is a Protein and Thus a Biological Product

52. The PHSA defines "biological product" to include a "protein." 42 U.S.C. § 262(i)(1).

53. As FDA acknowledged during the rulemaking process, there is no "clear scientific consensus for a particular number of amino acids to use when distinguishing between" proteins and other alpha amino acid-containing polymers. 85 Fed. Reg. at 10,059.

54. Retatrutide is a "protein" according to FDA's own regulatory definition, under which a product is a "protein" if it: (1) is an "alpha amino acid polymer," (2) has "a specific, defined sequence," and (3) "is greater than 40 amino acids in size," counting "the total number of amino acids" in the polymer that are "associated with each other in a manner that occurs in nature." 21 C.F.R. § 600.3(h)(6). Retatrutide satisfies each of those conditions.

55. **Alpha amino acid polymer**. Retatrutide is an "alpha amino acid polymer" because it is a polymer that contains alpha amino acids. Retatrutide comprises a backbone of 39 alpha amino acids and an associated chain of two additional amino acids, one of which (gamma-glutamate) is an alpha amino acid.

56. Irrespective of whether retatrutide's remaining amino acid (ADO) is an alpha amino acid, retatrutide is still an "alpha amino acid polymer." Nothing in FDA's regulations requires that an alpha amino acid polymer must be composed *solely* of alpha amino acids, and FDA has previously approved biologics licenses for products composed of a mix of alpha and non-alpha

amino acids. *See* Sogroya Prescribing Information § 11 (April 2023), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761156s005lbl.pdf. FDA thus did not dispute that retatrutide is an alpha amino acid polymer.

57. **Specific, defined sequence**. Retatrutide is synthesized according to "a pre-defined template" that results in an "identical sequence across batches." *Teva*, 514 F. Supp. 3d at 106. It accordingly has a "specific, defined sequence," *id.* (quoting 21 C.F.R. § 600.3(h)(6)), as FDA also did not contest.

58. **Greater than 40 amino acids in size**. Retatrutide has "more than 40 amino acids," all of which are in chains "associated with each other in a manner that occurs in nature." 21 C.F.R. § 600.3(h)(6).

59. Retatrutide's backbone comprises 39 amino acids. Its associated chain has two more. The associated chain connects to the backbone via an "isopeptide bond," which is "an amide bond between a carboxyl group of one amino acid and an amino group of another amino acid" that commonly occurs in nature. *See* Roger L. Lundblad, *Biochemistry and Molecular Biology Compendium* 175 (2019). FDA did not contest this conclusion either.

60. The "total number of amino acids in [retatrutide's] chains" is thus 41.

61. Retatrutide is "greater than 40 amino acids in size" even though one of its amino acids, ADO, is a non-alpha amino acid. 21 C.F.R. § 600.3(h)(6). FDA's regulation instructs that the count is based on "the total number of amino acids in [a product's] chains." *Id.* It does not limit the count to alpha amino acids. The "total number" means all, not just some.

62. Indeed, text and context make clear that all amino acids count. The requirement that a polymer must have "greater than 40 amino acids," and the instruction to sum "the total number of amino acids," follow the initial reference to "*alpha* amino acid polymer," but the latter

two instructions omit the word "alpha." *Id.* Principles of textual interpretation therefore require giving effect to the omissions. *See, e.g.*, *Barnhart v. Sigmon Coal Co.*, 534 U.S. 438, 452 (2002).

63. FDA has also expressed a preference for using its authority over biological products when handling relatively "complex" products. 85 Fed. Reg. 12,930, 12,931-32 (Mar. 5, 2020); *see Teva*, 514 F. Supp. 3d at 79 (explaining FDA's view that its "protein" definition is a "proxy for complexity"). Non-alpha amino acids (such as ADO) are often larger and more complex than alpha amino acids; for example, ADO has additional carbons (and oxygens) between the amino group and the carboxyl group compared to "alpha" amino acids as defined by FDA. Indeed, an approach that fails to count all alpha and non-alpha amino acids would mean that novel polymers of potentially *hundreds* of total amino acids would not count as proteins—despite the obvious complexity of such polymers—if only 40 of the amino acids were alpha amino acids. Nothing in FDA's regulations supports such a result.

64. In rejecting Lilly's position that retatrutide is a protein, FDA asserted that the definition can be satisfied only by polymers with "more than 40 *alpha* amino acids" (emphasis added). According to the agency, "the reference to 'alpha amino acid polymer' at the beginning of the definition makes clear that only alpha amino acids are relevant to determining whether something is a protein, which is consistent with commonly understood scientific principles." Neither the agency's textual analysis nor its appeal to supposed "commonly understood scientific principles" justifies its conclusion.

65. First, the definition's initial reference to "*alpha* amino acid polymers" does not in any way suggest that later references to "amino acids" are *also* limited to alpha amino acids. Indeed, "the general principle of [textual] construction" is the opposite—that "when [the drafter] includes particular language in one section of [a law] but omits it in another section of the same

[law], it is generally presumed that [the drafter] acts intentionally and purposely in the disparate inclusion or exclusion." *Barnhart*, 534 U.S. at 452 (cleaned up). And that presumption is particularly strong where, as here, the deliberate omission comes later within the *same sentence*.

66. Second, "commonly understood scientific principles" do not dictate that "only alpha amino acids are relevant to determining whether something is a protein." The agency emphasizes that "proteins of humans are synthesized almost exclusively from 20 alpha amino acids," but that fact also does not support FDA's position: The statutory and regulatory term "protein" is *not* limited to "proteins of humans," but plainly includes chemically synthesized proteins as well. Indeed, in 2019, Congress amended the definition of protein to remove the prior exclusion of "chemically synthesized polypeptides," thereby confirming that "protein" includes chemically synthesized polypeptide products. Pub. L. No. 116-94, Div. N, Tit. I, § 605, 133 Stat. 3127 (2019). The single source that FDA cites in support of its invocation of "commonly understood scientific principles," *see* Antonin Ginguay & Luc A. Cynober, *Amino Acids*, *in* Encyclopedia of Biological Chemistry (3d Ed. 2021), does not support the agency's position either (much less override Congress's choice to include chemically synthesized proteins). An entry in a biochemistry encyclopedia, it merely discusses the general role of alpha amino acids in various biological processes—without addressing the definition of a protein at all. Moreover, the agency's hedging language ("*almost* exclusively") concedes that non-alpha amino acids sometimes *are* used in the biosynthesis of proteins. *See* ¶ 56, *supra* (identifying approved biologics licenses for product composed of a mix of alpha and non-alpha amino acids).

67. FDA's rationale for counting only alpha amino acids is also internally inconsistent. Although FDA is correct that naturally occurring human proteins are synthesized almost exclusively from 20 common alpha amino acids, the agency's definition of a protein is not so

limited. Instead, the regulatory definition also includes polymers composed of *any* alpha amino acids—even those that do *not* naturally occur in humans. FDA has articulated no reason for *excluding* non-alpha amino acids on the ground that they are not involved in human protein synthesis, while *including* alpha amino acids that are similarly situated. FDA's internally inconsistent rationale cannot limit the regulatory definition's plain text.

68. FDA's definition of an "alpha amino acid" is also inconsistent with the agency's own reasoning in another respect: It excludes at least one of the 20 common amino acids involved in human protein synthesis. FDA asserted that 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." But proline—an amino acid used in natural human protein synthesis—also fails to meet this strict definition. *See* Ginguay & Cynober, *supra*, at 2 (proline's "–NH_2 group is part of a heterocycle," such that it lacks a standard amino group). FDA's focus on amino acids used to synthesize human proteins thus does not support its categorical exclusion of non-alpha amino acids.

69. In sum, the right conclusion is the straightforward one indicated by the regulation's text: Retatrutide is "greater than 40 amino acids in size," 21 C.F.R. § 600.3(h)(6), because it has more than 40 amino acids.

At Minimum, Retatrutide Is "Analogous" to a Protein

70. Independent of the fact that retatrutide qualifies as a protein, it qualifies as a biological product because it is at minimum an "analogous product" to a protein.

71. Under the PHSA, "a protein, or analogous product" is a "biological product." PHSA § 351(i)(1). The statute does not define "analogous product," nor has FDA adopted a regulation or guidance document defining products analogous to proteins. Notably, FDA regulations define what it means for a product to be "analogous" to a "virus," to a "therapeutic serum," or to a "toxin

or antitoxin," 21 C.F.R. § 600.3(h)(5)(i)-(iii), but the regulations do not at all address the statutory category of products that are analogous to proteins.

72. As a matter of plain meaning, a product is "analogous" to a protein when it is "similar or comparable" to a protein "either in general or in some specific detail." *Ipsen Biopharmaceuticals, Inc. v. Becerra*, No. 22-CV-860, 2023 WL 3319366, at *13 (D.D.C. May 8, 2023) (referring to *Analogous*, Merriam-Webster Dictionary, https://tinyurl.com/y49khdfa). FDA has similarly taken the position in litigation that a product is analogous to proteins when it "share[s] some defining features with proteins." *Teva*, 514 F. Supp. 3d at 113 (characterizing FDA's position).

73. Retatrutide is "analogous" to a protein because it is similar to other proteins in structure, complexity, and function. Retatrutide contains 41 total amino acids in a specific, defined sequence, and the vast majority of those (40 of them) are alpha amino acids. It also shares structural and functional characteristics in common with a protein comprising 41 alpha amino acids. Like other proteins, retatrutide has a consistent three-dimensional structure, including a clear alpha helical structure that is characteristic of proteins, and it has structural features similar to the 42-amino acid glucose-dependent insulinotropic polypeptide (GIP), which is a naturally occurring protein hormone. As noted, retatrutide's two-amino-acid chain of ADO and gamma-glutamate (along with an associated fatty acid) serves important functions, including facilitating binding to albumin to extend pharmacokinetic half-life, while simultaneously providing desired pharmacological properties—namely, receptor agonism, which is a typical function of proteins.

74. FDA has identified mixtures of a protein and a lipid as an example of an "analogous product" to a protein. *Ipsen*, 2023 WL 3319366, at *13. Retatrutide is more similar to a protein composed of 41 alpha amino acids than are such mixtures.

75. In sum, an alpha amino acid polymer that contains 41 amino acids; and of those, 40 (97.6%) are *alpha* amino acids. It should therefore at a minimum be considered "analogous" to a protein that contains 41 alpha amino acids. Retatrutide is analogous to a protein in all meaningful respects, which provides another independent reason why FDA should classify retatrutide as a biological product.

76. In rejecting Lilly's position that retatrutide is at least analogous to a protein, FDA took the blanket position that *no* "alpha amino acid polymers with fewer than 41 alpha amino acids" may *ever* qualify as a protein—regardless of whether the product is analogous to a protein in every other relevant respect. To accept any product that fails to satisfy the "protein" definition in Section 600.3(h)(6), the agency argued, "would undo the bright line principle established by the rule," with the result that "FDA would frequently have to evaluate on a case-by-case basis the features of a particular molecule to determine if it is analogous to a protein."

77. FDA's determination that retatrutide cannot be "analogous" to a protein unless it satisfies the definition of protein largely reads the word "analogous" out of the statute and therefore fails as a matter of law. By creating a separate category for "analogous" products, Congress expressly demonstrated its intention to include some products that do *not* otherwise fit into the previously enumerated categories, including those that do not meet FDA's definition of a protein.

78. FDA has identified only a single type of substance that it considers "analogous" to a protein: "naturally derived mixtures that include identified biological product components (e.g., protein) *and* identified non-biological product components that can contribute to the product's activity" (emphasis added). In FDA's view, "the naturally derived mixture [is] 'analogous' to a protein if the identified biological product component (the protein) in the mixture is necessary for the activity of the product and contributes to achieving the intended therapeutic

effect of the product." In other words, the sole product that FDA considers "analogous" to a protein is a mixture that contains a protein.

79. That makes little sense. The word "analogous" does not mean "contains," nor has FDA identified any basis for defining it that way. Dictionaries define "analogous" to mean "showing an analogy or a likeness permitting one to draw an analogy: susceptible of comparison either in general or in some specific detail." *Analogous*, Webster's Third New Int'l Dictionary 77 (2002). That differs significantly from the meaning of "contain," which is "to have within" or "to consist of wholly or in part." *Contain*, Webster's Third New Int'l Dictionary 490-91. Thus, although it may be true that *some* products analogous to a protein will contain a protein, it is simply not true that *all* products analogous to a protein will contain a protein.

80. FDA's attempt to unduly restrict the scope of "analogous" to mean only "contains" with respect to proteins also requires the word "analogous" to take on multiple, inconsistent definitions within the statutory scheme. The statutory definition of biological product uses the word "analogous" only once: "The term 'biological product' means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, *or analogous product*." 42 U.S.C. § 262(i)(1) (emphasis added). For several of those categories, FDA has defined what it means to be an "analogous" product—and it has defined the analogous product to include substances that *do not* contain a component that itself satisfies the category's definition.

81. For instance, a product is an antitoxin only if it "contain[s] the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune." 21 C.F.R. § 600.3(h)(4). But a product is *analogous* to an antitoxin if it is "intended, *irrespective of its source of origin*, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process." *Id.* § 600.3(h)(5)(iii)

(emphasis added). Products can similarly be "analogous" to a virus or therapeutic serum without containing a virus or therapeutic serum, and also without satisfying all elements of the definition of those terms. *See id.* § 600.3(h)(5)(i) (product analogous to virus if "prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used"); *id.* § 600.3(h)(5)(ii) (product analogous to therapeutic serum "if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum").

82. By adopting one definition of "analogous" for products analogous to a protein ("contains"), but a different definition for products analogous to other protein categories, FDA would "attribute different meanings to the same [word] in the same sentence, depending on which object it is modifying." *Reno v. Bossier Parish School Bd.*, 528 U.S. 320, 329 (2000). As the Supreme Court has explained, courts must "refuse to adopt [such] a construction." *Id.*

83. FDA's attempt to piggyback on its own "protein" definition in determining what qualifies as an analogous product is particularly suspect given that courts, not the agency, bear ultimate responsibility for the "legal interpretation" of both of these statutory terms. *Loper Bright*, 144 S. Ct. at 2268; *see id.* at 2296 (Kagan, J., dissenting) (identifying the definition of "'biological product[s],' including 'protein[s]'" and analogous products, as an interpretative question that courts must now resolve) (quoting 42 U.S.C. § 262(i)(1)). As the agency has recognized, no "clear scientific consensus" limits proteins to polymers comprising "a particular number of amino acids." 85 Fed. Reg. at 10,059. Instead, the agency adopted its "bright-line rule" for proteins largely for policy reasons, including to "facilitate[] implementation" and "provide[] regulatory clarity." *Id.* FDA's categorical determination that if a product fails to satisfy its "protein" definition, it therefore

also cannot be *analogous* to a protein elevates the agency's policy preference for a bright-line rule above the statute's command.

84. Nor may FDA rewrite the statutory text based on a desire to avoid "frequently hav[ing] to evaluate on a case-by-case basis the features of a particular molecule to determine if it is analogous to a protein." The agency may establish general rules for identifying products analogous to proteins—as it has done for identifying products analogous to viruses, therapeutic serums, and toxins and antitoxins. 21 C.F.R. § 600.3(h)(5)(i)-(iii). But a disinclination to consider analogous products "on a case-by-case basis" as a policy matter cannot justify effectively reading analogous products out of the statute altogether. Courts must "interpret statutes, no matter the context, based on the traditional tools of statutory construction, not individual policy preferences." *Loper Bright*, 144 S. Ct. at 2268.

85. For these reasons, this case stands in stark contrast to the D.C. Circuit's recent decision in *Ipsen Biopharmaceuticals, Inc. v. Becerra*, 108 F.4th 836 (2024). For one thing, the court there "agree[d] . . . that 'analogous product' includes 'analogous proteins.'" *Id.* at 845. And while the court rejected a challenge to FDA's determination that lanreotide acetate, a polymer composed of just *eight* amino acids, and found that it was not analogous to a protein, *id.* at 846, "[n]otably, Ipsen d[id] not argue the FDA's decision or approach conflicts with the ordinary meaning of analogous." *Id.* Lilly argues precisely that here.

86. In *Ipsen*, moreover, the court relied on FDA's representation that it "will make case-by-case determinations" about whether particular products shared "critical characteristics" with proteins. *Id.* at 846. But FDA has done the opposite here: It has rejected retatrutide under its "bright line" rule in order to *avoid* "frequently hav[ing] to evaluate on a case-by-case basis the features of a particular molecule to determine if it is analogous to a protein." That "bright line" rule conflicts

with the statute's text and, on FDA's own telling, rests on considerations of convenience, *not* any supposed "scientific expertise." *Ipsen*, 108 F.4th at 846. Indeed, nothing in FDA's decision about whether retatrutide is analogous involves *any* scientific analysis—just a legal conclusion that *no* "alpha amino acid polymers with fewer than 41 alpha amino acids" may *ever* qualify as "analogous" to a protein. *See Loper Bright*, 144 S. Ct. at 2268 ("legal interpretation" deserves no deference).

FDA's Refusal to Designate Retatrutide as a Biological Product Harms Lilly

87. FDA's improper classification of retatrutide has significant implications for Lilly. Biological products and drugs are subject to approval under different statutory authorities with different substantive and procedural requirements. *Compare* 42 U.S.C. § 262(a) (licensure standards for biologic license applications) *and* 21 C.F.R. § 601.2 (procedures and content requirements for biologic license applications), *with* 21 U.S.C. § 355(d) (approval standards for new drug applications) *and* 21 C.F.R. § 314.50 (content requirements and procedures for new drug applications). Once a new biological product or drug is approved, different rules govern critical aspects of its marketing. Products approved pursuant to biologics license applications, for example, enjoy a longer period of statutory exclusivity than those approved pursuant to new drug applications. *Compare* 42 U.S.C. § 262(k)(7), *with* 21 U.S.C. §§ 355(c)(3)(E), (j)(5)(F). Biological products and drugs are also subject to different timelines for selection into the Inflation Reduction Act's "Drug Price Negotiation Program." *Compare* 42 U.S.C. § 1320f-1(e)(1)(B)(ii) (biological products eligible for selection 11 years after licensure), *with* 42 U.S.C. § 1320f-1(e)(1)(A)(ii) (drugs eligible for selection 7 years after approval). And biological products are ineligible for exemptions for compounded drugs under the FDCA. *See* 21 U.S.C. §§ 353a, 353b. These

differences in regulatory treatment have substantial ramifications for Lilly at nearly every stage of retatrutide's development, licensure, and marketing.

The Court Cannot Remand Now Because the Statutory Deadline Lapsed

88. Congress directed FDA to resolve a classification request "[n]ot later than 60 days after the receipt of the request." 21 U.S.C. § 360bbb-2(b). This statutory command, which twice uses "shall," is mandatory and non-extendable. *See FTC v. Tarriff*, 584 F.3d 1088, 1090 (D.C. Cir. 2009) ("It is . . . fixed usage that 'shall' means something on the order of 'must' or 'will.'"). Congress also specified that the agency's failure to comply with the statutory deadline automatically results in acceptance of the requested classification. *Id.* § 360bbb-2(c). In light of the substantially different requirements that govern biologic license applications and new drug applications, moreover, adherence to the 60-day deadline is necessary to ensure that a product's sponsor knows with sufficient lead-time which regulatory framework it must satisfy.

89. A marketing application also must contain different types of data depending on whether it a New Drug Application for a drug or a Biologics License Application for a biological product. An applicant must know the type of application a year or more in advance of submission in order to begin its preparation.

90. Crucially, in the face of this clear command to resolve an RFD within the 60-day deadline, FDA's response to Lilly's RFD did not dispute Lilly's position on several key issues.

a. In rejecting Lilly's argument that retatrutide is a protein, FDA stated that the agency was "assum[ing] (without conceding) that retatrutide has a specific defined sequence," "assum[ing] that ADO is an amino acid," and "assum[ing], 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."

b. In rejecting Lilly's alternative argument that retatrutide is analogous to a protein, FDA asserted that "being greater than 40 alpha amino acids is a fundamental, defining property of a protein" and that "retatrutide cannot be analogous to a protein because it does not share this fundamental defining property." But FDA did not claim that retatrutide is disanalogous to a protein any other respect.

91. If this Court agrees with Lilly that FDA's reasons for rejecting Lilly's RFD are erroneous, then the Court should not remand to FDA to give the agency another opportunity to identify new aspects of Lilly's recommendation with which it disagrees. Instead, the Court should direct Defendants to designate retatrutide as a biological product.

92. Any other resolution would reward FDA for failing to resolve all aspects of Lilly's request within the statutory deadline. It would also encourage the agency to provide partial responses to RFDs: By rejecting *some* aspects of a request for designation—but assuming other aspects of the request without deciding them—the agency would give itself another chance to come up with reasons to reject the request in the event that a court finds its initial reasons to be invalid. The result would be a drawn-out process that far exceeds the mandatory 60-day deadline that Congress set for resolving RFDs, which does not contemplate that FDA might resolve an RFD only partially.

93. Indeed, if this Court sets aside FDA's response to Lilly's RFD because the only grounds identified by the agency are found to be erroneous, then the agency would not have "determine[d] the classification of the product" through any valid agency action. 21 U.S.C. § 360bbb-2(b). As a consequence, the statutory deadline would long since have lapsed, and "the

recommendation made by" Lilly must "be considered to be a final determination" of retatrutide's classification. *Id.* § 360bbb-2(c).

CLAIMS FOR RELIEF

FIRST CLAIM FOR RELIEF

Violation of the Administrative Procedure Act
(Declaratory/Injunctive Relief – FDA's Refusal to Designate Retatrutide as a Biological Product Exceeds the Agency's Statutory Authority)

94. Lilly realleges and incorporates by reference all prior and subsequent paragraphs.

95. The APA requires courts to "hold unlawful and set aside agency action" that is "not in accordance with law," 5 U.S.C. § 706(2)(A), or is "in excess of statutory jurisdiction, authority, or limitations," *id.* § 706(2)(C).

96. Under the PHSA, FDA must regulate as a "biological product" any "protein" or "analogous product." 42 U.S.C. § 262(i)(1).

97. Retatrutide is a protein or analogous product. FDA's denial of Lilly's request to designate retatrutide as a biological product accordingly must be set aside.

SECOND CLAIM FOR RELIEF

Violation of the Administrative Procedure Act
(Declaratory/Injunctive Relief – FDA's Refusal to Designate Retatrutide as a Biological Product Violates the Agency's Own Regulations)

98. Plaintiff realleges and incorporates by reference all prior and subsequent paragraphs.

99. An agency is "bound" to follow its own rules. *Clean Air Council v. Pruitt*, 862 F.3d 1, 9 (D.C. Cir. 2017) (citation omitted). An agency's failure to do so is arbitrary and capricious, *see National Cable & Telecomm. Assn. v. Brand X Internet Servs.*, 545 U.S. 967, 981 (2005); is "not in accordance with law," 5 U.S.C. § 706(2)(A); and constitutes agency action "without

observance of procedure required by law," *id.* § 706(2)(D). It also violates due process and general principles of administrative law.

100. FDA has promulgated a rule defining "protein" as an "alpha amino acid polymer" with a "specific, defined sequence" that has "more than 40 amino acids," counting "the total number of amino acids" in chains that are "associated with each other in a manner that occurs in nature." 21 C.F.R. § 600.3(h)(6).

101. Retatrutide satisfies each component of that definition.

102. FDA's denial of Lilly's request to designate retatrutide as a protein, and hence as a biological product, violates the agency's own regulations and must be set aside.

THIRD CLAIM FOR RELIEF

Violation of the Administrative Procedure Act
(Declaratory/Injunctive Relief – FDA's Refusal to Designate Retatrutide as a Biological Product is Arbitrary, Capricious, and an Abuse of Discretion)

103. Lilly realleges and incorporates by reference all prior and subsequent paragraphs.

104. The APA requires a court to "hold unlawful and set aside agency action" that is "arbitrary, capricious, [or] an abuse of discretion." *Id.* § 706(2)(A).

105. Agency action meets that standard when the agency relies on impermissible factors or fails to consider important factors; gives an inadequate, implausible, or counterintuitive explanation for its decision; or fails to explain why it has treated similarly situated entities differently. *See, e.g.*, *Am. Bankers Ass'n v. Nat'l Credit Union Admin.*, 934 F.3d 649, 663 (D.C. Cir. 2019); *Cal. Cmtys. Against Toxics v. EPA*, 928 F.3d 1041, 1057 (D.C. Cir. 2019).

106. FDA's justifications for failing to designate retatrutide as a "protein" or an "analogous product" are arbitrary and capricious and an abuse of discretion.

107. FDA's denial of Lilly's request for designation of retatrutide as a biological product must accordingly be set aside.

PRAYER FOR RELIEF

NOW, THEREFORE, Plaintiff Eli Lilly requests a judgment in its favor against Defendants as follows:

1. Declare that Defendants' denial of Plaintiff's request for designation of retatrutide as a biological product is arbitrary and capricious, an abuse of discretion, and unlawful under the APA and the applicable governing statutes;

2. Enter an injunction requiring Defendants to designate retatrutide as a biological product;

3. Award Plaintiff reasonable attorneys' fees and costs; and

4. Grant such other and further relief as the Court may deem appropriate.

Dated: September 3, 2024

Respectfully submitted,

/s/ *Jayna M. Cacioppo*

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CERTIFICATE OF SERVICE

I hereby certify that this document will be served on Defendants in accordance with Fed. R. Civ. P. 4.

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