United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued April 1, 2024

Decided July 9, 2024
Reissued July 25, 2024

No. 23-5142

IPSEN BIOPHARMACEUTICALS, INC.,
APPELLANT

v.

XAVIER BECERRA, IN HIS OFFICIAL CAPACITY AS SECRETARY OF HEALTH AND HUMAN SERVICES, ET AL.,
APPELLEES

Appeal from the United States District Court
for the District of Columbia
(No. 1:22-cv-00860)

Catherine E. Stetson argued the cause for appellant. With her on the briefs were *Susan M. Cook*, *Marlan Golden*, and *Dana A. Raphael*.

Urja Mittal, Attorney, U.S. Department of Justice, argued the cause for federal appellees. With her on the brief were *Brian M. Boynton*, Principal Deputy Assistant Attorney General, *Daniel Tenny*, Attorney, and *Samuel R. Bagenstos*, General Counsel, U.S. Department of Health & Human

Services. *Anna O. Mohan*, Senior Counsel, U.S. Department of Justice, entered an appearance.

Brian T. Burgess argued the cause for appellee InvaGen Pharmaceuticals, Inc. With him on the brief was *Gerard J. Cedrone*.

Before: WILKINS, KATSAS and RAO, *Circuit Judges*.

Opinion for the Court filed by *Circuit Judge* WILKINS.

WILKINS, *Circuit Judge*: In 2007, the Food and Drug Administration ("FDA") approved Ipsen Biopharmaceuticals, Inc.'s application to sell Somatuline Depot as a drug product under the Federal Food, Drug, and Cosmetic Act ("FDCA"). This approval gave Somatuline Depot a period of market exclusivity, and the FDA did not authorize any competing generic forms of the drug for over a decade.

That changed in 2021 when the FDA approved an application filed by InvaGen Pharmaceuticals, Inc., one of Ipsen's competitors, to sell a generic version of Somatuline Depot under the FDCA. This approval ended Somatuline Depot's era of market exclusivity. At the heart of this dispute, is Ipsen's belief that Somatuline Depot should still enjoy market exclusivity.

Here, Ipsen argues that the FDA's classification of its product violated the Administrative Procedure Act ("APA"). In Ipsen's view, Somatuline Depot is not a drug product subject to the FDCA; it is a biologic and must be regulated under the Public Health Service Act ("PHSA"). Had the FDA correctly regulated Somatuline Depot, Ipsen further argues, the FDA could not have approved InvaGen's application under the FDCA.

Two of Ipsen's prayers for relief are relevant to this appeal: (1) declaratory judgment that the FDA's refusal to reclassify Somatuline Depot as a biologic was arbitrary, capricious, and contrary to law in violation of the APA, and (2) vacatur of the FDA's approval of InvaGen's application to sell a generic version of Somatuline Depot. The District Court rejected Ipsen's arguments and granted summary judgment to the government and InvaGen, which intervened to defend its interest in keeping the generic Somatuline Depot on the market. We agree with the result and, for reasons explained in the opinion, affirm.

I.

A.

This case involves two statutory schemes, and a few regulations, that establish the processes for obtaining FDA approval of drug products and biological products. Both drugs at issue in this case (Ipsen's and InvaGen's, respectively) were approved under the FDCA, which governs drugs. But Ipsen wants the FDA to reclassify its drug, Somatuline Depot, as a biologic subject to the PHSA. If such a reclassification were to occur, the FDA's approval of InvaGen's generic version of Somatuline Depot could be jeopardized. The difference in the statutory schemes explains why.

We begin with the FDCA. It forbids the sale of "any new drug" without FDA approval. 21 U.S.C. § 355(a). This approval is conditioned on the FDA evaluating the application to sell the drug and, ultimately, concluding that the drug is safe and effective for its intended uses. *Id.* § 355(b)(1)(A), 355(d)(2). Two of the FDCA's three pathways to FDA approval are relevant here: the innovator pathway and the generic pathway.

Ipsen took the innovator pathway: it filed a New Drug Application and included its own clinical data that demonstrated Somatuline Depot's efficacy and safety. *See id.* § 355(b)(1). After receiving FDA approval, Ipsen, as an innovator, enjoyed a period of market exclusivity where it sold Somatuline Depot without having to compete with any generic forms of the drug.

InvaGen, however, took a generic pathway that became available once Ipsen's exclusivity period concluded. In taking this route, InvaGen's application demonstrated that its product had the same "active ingredient, route of administration, indication, dosages and strengths" of Somatuline Depot. J.A. 28. Because Somatuline Depot served as the reference product, InvaGen was able to show its product's efficacy and safety by relying on the same clinical research that Ipsen provided to the FDA. *See* 21 U.S.C. § 355(b)(2).

We can now turn to the PHSA, which shares some similarities with the FDCA. *See* 42 U.S.C. § 262. Similar to approval under the FDCA, one pathway to approval under the PHSA requires the manufacturer to demonstrate that its product is "safe, pure, and potent" and its production facility is "designed to assure that the biological product continues to be safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i)(I)–(II). The PHSA's other approval pathway is, likewise, similar to the FDCA in that it permits a manufacturer to show that its product is "highly similar to the reference product" by submitting data that shows that "there are no clinically meaningful differences between the biological product and the reference product in terms of … safety, purity, and potency." *Id.* § 262(i)(2). We note a final similarity between the two approval processes: when determining what the product is (a drug or biologic) the FDA analyzes the product's "active ingredient," defined as "any component that is intended to furnish pharmacological

activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease." 21 C.F.R. § 314.3(b).

But there is also a significant difference in the two approval processes. Under the PHSA, unlike the FDCA, manufacturers must conduct their own clinical studies. This distinction in approval processes sits at the crux of this case. If Somatuline Depot were regulated under the PHSA, then InvaGen's generic product would not have been able to use Ipsen's clinical studies to achieve FDA approval. The PHSA does not permit piggybacking.

The difference in approval processes makes sense. Biologics are "a type of drug derived from natural, biological sources such as animals or microorganisms. Biologics thus differ from traditional drugs, which are typically synthesized from chemicals." *Sandoz, Inc. v. Amgen Inc.*, 582 U.S. 1, 6 (2017). Indeed, a "biological product" is narrowly defined under the PHSA as a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product … applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i)(1). Whereas the FDCA defines a "drug" more broadly as an "article[] intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man" or "intended to affect the structure or any function of the body of man." 21 U.S.C. § 321(g)(1)(B), (C).

The type of biological products that are relevant here are proteins and analogous products. The FDA defines a "protein" as "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 … will be based on the total

number of amino acids in those chains." 21 C.F.R. § 600.3(h)(6). The FDA has not provided a definition for a product that is "analogous" to a protein, and instead leaves itself the space to make case-by-case determinations. J.A. 480–81. At a minimum, however, the FDA takes the position that a product that is analogous to a protein shares its "critical characteristics." J.A. 480.

B.

Ipsen's drug, Somatuline Depot, "effects an extended-release dosing of its active ingredient lanreotide acetate, a molecule that mimics the naturally occurring hormone somatostatin." *Ipsen Biopharmaceuticals, Inc. v. Becerra*, 678 F. Supp. 3d 20, 27 (D.D.C. 2023) (internal quotation marks omitted) (*Ipsen II*). During manufacture, the lanreotide acetate (an eight amino acid polymer) in Somatuline Depot assembles into structures known as nanotubes. The solution is then injected into the body where it forms a depot under the skin that "diffuses specific amounts of lanreotide into circulation in the body over an extended period of time." *Id.* at 39 (internal quotation marks omitted). Recall that the FDA approved, and regulates, Somatuline Depot as a drug under the FDCA.

In March 2020, pursuant to the Biologics Price Competition and Innovation Act, the FDA reclassified drugs that were originally approved and regulated under the FDCA to "biological products" under the PHSA if these products met the PHSA's definition of a biological product. Somatuline Depot did not make the cut. In response, Ipsen asked the FDA to reconsider its decision to leave Somatuline Depot off of the reclassification list. The FDA refused Ipsen's reconsideration request. So Ipsen sued. It argued that the FDA's refusal to transition Somatuline Depot from a drug product to a biological product violated the APA. *See Ipsen Biopharmaceuticals, Inc.*

v. Becerra, No. 20-cv-2437, 2021 WL 4399531, at *3 (D.D.C. Sept. 24, 2021).

In September 2021, the District Court dismissed that suit because Ipsen did not have standing. Relevant here is the District Court's conclusion that Ipsen's lawsuit rested on a "highly speculative fear that" at least one company would apply to "market a generic version of Somatuline Depot," that the FDA would approve such an application, and the approved generic version would not satisfy the PHSA's demanding requirement to show that it is highly similar to Somatuline Depot. *Id.* at *4 (internal quotation marks omitted). In short, Ipsen could not demonstrate that the FDA's refusal to reclassify Somatuline Depot constituted an injury because there was no generic version of Somatuline Depot on the market.

But a few months later, in December, the FDA approved InvaGen's application to sell a generic version of Somatuline Depot. In response, Ipsen sued the FDA again. As it did in its previous suit, Ipsen argued that when Somatuline Depot is in its final dosage form, the lanreotide acetate assembles into nanotube structures in a manner that occurs in nature and, once in these nanotube assemblies, the lanreotide acetate chains have over forty amino acids. *See Ipsen II*, 678 F. Supp. 3d at 35–36. The FDA's conclusion to the contrary, Ipsen argued, violated the APA because it was arbitrary and capricious. *See* 5 U.S.C. § 706(2)(A). In the alternative, Ipsen argued that Somatuline Depot was analogous to a protein, and the FDA's interpretation and application of Section 262(i)(1) concluding otherwise violated the APA because it was not in accordance with law. *Id.*; *see also Ipsen II*, 678 F. Supp. 3d at 40.

This time, assured of its jurisdiction under Article III and the federal question statute, *see* 28 U.S.C. § 1331, the District

Court resolved the case at summary judgment[1] in favor of the FDA and InvaGen. First, the District Court rejected Ipsen's argument that the FDA was legally required to evaluate whether lanreotide acetate had over eight amino acids in Somatuline Depot's final dosage form. *See Ipsen II*, 678 F. Supp. 3d at 36–38. It also rejected Ipsen's argument that Somatuline Depot is a protein because, the District Court found, Somatuline Depot's active ingredient, lanreotide acetate, is an eight amino acid chain; and eight is less than forty. *Id.* at 38–40. Last, the District Court rejected Ipsen's argument that the FDA's interpretation of "analogous" to a protein, under Section 262(i)(1), rendered the word "analogous" superfluous. *Id.* at 40–41. Having rejected all of Ipsen's arguments, the District Court concluded that the FDA's decision to regulate Somatuline Depot as a drug product did not violate the APA. *Id.* at 41. This appeal followed.

II.

We begin with Ipsen's lead argument: the FDA's refusal to transition Somatuline Depot to regulation as a biological product was "arbitrary" and "capricious" in violation of the APA. In analyzing the FDA's decision, we "must be careful not to unduly second-guess an agency's scientific judgments," and will affirm the FDA's decision so long as it is "reasonable and reasonably explained." *Cytori Therapeutics, Inc. v. FDA*, 715 F.3d 922, 923, 926 (D.C. Cir. 2013); *see also Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). We begin with the parties' multiple points of

[1] This was a final judgment that gives rise to our jurisdiction under 28 U.S.C. § 1291. We review this judgment de novo. *See Cigar Ass'n of Am. v. FDA*, 964 F.3d 56, 61 (D.C. Cir. 2020) ("When a district court reviews agency action under the APA, we in turn review the district court's decision de novo.").

agreement so that we can clearly articulate the precise issue that we are asked to resolve.

The parties largely agree on the law. All agree that the relevant statute is 42 U.S.C. § 262(i)(1), which recognizes that a protein is a biological product. Ipsen also does not challenge the FDA's final rule defining a protein as "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 … will be based on the total number of amino acids in those chains." 21 C.F.R. § 600.3(h)(6). The parties further agree that the relevant question is whether a drug's active ingredient meets the FDA's definition of a protein. And all are in accord that an "active ingredient" is "any component that is intended to furnish pharmacological activity." 21 C.F.R. § 314.3(b).

There is similarly broad agreement on how the law applies to the facts. All agree that Somatuline Depot's active ingredient is lanreotide acetate. There is no dispute that lanreotide acetate is an "octapeptide" that contains eight amino acids. J.A. 469. The parties also agree that when Somatuline Depot is in its finished dosage form, the lanreotide acetate is organized into a nanotube structure that contains more than 40 amino acids, but the nanotubes themselves do not confer any pharmacological effect. *See* J.A. 472–74; Oral Arg. 2:55–3:30.

Given the extent of agreement on both facts and law, the FDA and InvaGen advance an intuitive and straightforward argument: the FDA reasonably concluded and adequately explained that the nanotube structures do not confer any pharmacological effect; therefore, Somatuline Depot's active ingredient is simply lanreotide acetate—an eight amino acid

chain. Because eight is less than forty, lanreotide acetate is not a protein, and Somatuline Depot is not a biologic. Case closed.

Alas, we find disagreement. In Ipsen's view, the FDA and InvaGen have ignored Section 262(i)'s relevant reference point: the biological *product*. "Product," Ipsen posits, refers to a "drug product," which the FDA defines as "a finished dosage form." 21 C.F.R. § 314.3(b). Putting these two definitions together, Ipsen argues that the FDA was required to count Somatuline Depot's amino acids in its final dosage form. And in the final dosage form, lanreotide acetate is organized into nanotube structures "in a manner that occurs in nature." 21 C.F.R. § 600.3(h)(6). From these premises, two conclusions necessarily follow: (1) these nanotube structures in Somatuline Depot's final dosage form contain over forty amino acids, therefore (2) lanreotide acetate is a protein, and Somatuline Depot is a biologic.

From this disagreement, we find the question presented: Did Congress silently incorporate the FDA's definition of a "drug product" under 21 C.F.R. § 314.3(b) into its definition of a "biological product" under 42 U.S.C. § 262(i)? As with all questions of statutory interpretation, "we begin with the text." *City of Clarksville v. FERC*, 888 F.3d 477, 482 (D.C. Cir. 2018); *see also Sandoz Inc. v. Becerra*, 57 F.4th 272, 280 (D.C. Cir. 2023). Here, we start with the Congress's separate definitions for a "drug," and a "drug product" under the FDCA. *Compare* 21 U.S.C. § 321(g)(1) (defining a drug) *with id.* § 321(dd) (defining drug product).

Congress defines a "drug" as an "article[] intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man" or "intended to affect the structure or any function of the body of man." *Id.* § 321(g)(1)(B), (C). And to determine whether an "article" is a "drug," the FDA looks to the "active ingredient," i.e., "any component that is intended to

furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man." 21 C.F.R. § 314.3.

The definition of a drug product, however, has nothing to do with the drug's impact on the body. Rather, it cross-references other statutory schemes that set forth the procedures that manufacturers follow to receive FDA approval: "For purposes of sections 335a and 335b of this title, the term 'drug product' means a drug subject to regulation under section 355, 360b, or 382 of this title or under section 262 of Title 42." *Id.* § 321(dd). In turn, the FDA defines a drug product as "a finished dosage form, e.g., tablet, capsule, or solution, that *contains a drug substance*, generally, but not necessarily, in association with one or more other ingredients." 21 C.F.R. § 314.3(b) (emphasis added).

From these two definitions and regulations, we identify an important distinction: a *drug* furnishes pharmacological activity, but a drug *product* is the "thing" ingested or administered. Said another way, you must ingest the drug product to reap the drug's benefits. The FDA regulates both, drugs and drug products. Hence, when a manufacturer applies for new drug approval, the manufacturer can identify the "drug substance (active ingredient) patent *or* a drug product (formulation or composition) patent." 21 U.S.C. § 355(b)(1)(A)(viii)(I) (emphasis added).

To better understand this distinction, consider Tylenol Cold and Flu medicine. The active ingredients in Tylenol Cold and Flu are acetaminophen, dextromethorphan, guaifenesin, and phenylephrine. *Label: Tylenol Cold Plus Flu Severe and Tylenol Cold Max*, NAT'L LIBR. MED., https://perma.cc/DG6P-54ZZ. And these active ingredients remain the same whether the drug is ingested as a liquid, *see id.*, or as a tablet, *see Label:*

Tylenol Cold and Flu-acetaminphen tablet, film coated, NAT'L LIBR. MED., https://perma.cc/3UJF-GPWN. But Tylenol Cold and Flu as a liquid is a different drug *product* than Tylenol Cold and Flu as a tablet—even though both, liquid and tablet, are the same *drug*.

Thus, we see two critical takeaways. First, the FDA does not determine whether Tylenol Cold and Flu (or any other product) is a drug by looking at its final dosage form. That decision is made by looking at the drug's active ingredient. Full stop. Second, the FDA must determine whether the "drug is safe for use and whether such drug is effective *in use*." 21 U.S.C. § 355(b)(1)(A)(i) (emphasis added); *see also id.* § 355(d), (e). This requires analyzing the drug product. Indeed, Tylenol Cold and Flu is approved for use as a solution or a tablet—and in both events remains the same drug—but there is no eye drop version of the drug product.

Now let's turn to a biological product, which Congress defines 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." 42 U.S.C. § 262(i)(1) (emphasis added).

This definition clearly shows that a "biological product" is quite distinguishable from a "drug product." Congress explicitly identified an "analogous product" as one example of a "biological product." This identification supports the FDA's reasoning that each of the items specified in the preceding list is itself a "product." Indeed, a "protein," like a "virus," a "therapeutic serum," or an "antitoxin," is itself a "product" within the scope of Congress's definition of a "biological product."

The fact that Congress instructs the FDA to regulate biological products as "drug products" is not at all inconsistent with our read of the statute. 42 U.S.C. § 262(j). Our critical takeaways are instructive, once again. The FDA must first determine whether the product is a "biologic," then it must examine how the biologic is ingested or administered—that is, how the biologic operates in *use* to determine if the product is "safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i)(I). In Ipsen's case, whether Somatuline Depot is "safe, pure, and potent" in its finished dosage form is a separate question from whether it is a "biological product."

Recall that the parties agree that the FDA must look to the active ingredient to determine whether a product is a biologic; here, lanreotide acetate, an eight amino acid chain. While Ipsen argues that the FDA's refusal to analyze lanreotide acetate when it is in nanotube structures was arbitrary and capricious, it does not dispute the FDA's scientific conclusion that these nanotubes have no pharmacological effect. And we all know that eight is less than forty, therefore, lanreotide acetate is not a protein. The FDA and InvaGen are correct: Case closed.

Ipsen's attempt to merge the FDA's definition of a "drug product," from a regulation interpreting a different statute, to trump the definition of a "biological product" specified by Congress in the relevant statute just does not work. This much is evident by simply looking to Ipsen's submissions to the FDA when it sought to have Somatuline Depot approved as a new drug. In that application, Ipsen relied on studies involving other formulations of lanreotide acetate, including an immediate-release version that did not assemble into nanotubes. Or put plainly, no matter the finished dosage form—whether in nanotube structures or otherwise—lanreotide acetate's pharmacological effect remained the same. J.A. 472–73.

And there's the rub. Under Ipsen's argument, Somatuline Depot qualifies as a biological product when it is evaluated in its finished dosage form. But other products, with the same active ingredient, would remain as drug products. What text supports this contradiction? After all, we see that Tylenol, no matter its finished dosage form, remains a drug.

Ipsen cannot resolve the killer contradiction that its argument compels. At best, Ipsen argues that a biological product must be evaluated as if it were a drug product because, in the preamble to the proposed rule defining a biological product, the FDA explained that "the associated amino acid chains 'would be added together to determine whether *the product* meets the numerical threshold.'" Ipsen Br. at 28 (quoting J.A. 294). But that argument falls flat because the final rule includes no such explanation. And Ipsen does not argue that the FDA violated the APA because the final rule was not the logical outgrowth of the proposed rule. *See, e.g.*, *Shell Oil Co. v. EPA*, 950 F.2d 741, 747 (D.C. Cir. 1991).

Scouring for a different textual hook, Ipsen cites to 42 U.S.C. § 262(j) and 21 U.S.C. § 321(g) and argues that biological products are merely types of drug products under those statutes. Ipsen Reply at 7. But even so, that does not mean Congress silently incorporated the FDA's definition of a "drug product" into the definition of a "biological product." More importantly, it does not indicate that biological products should be classified based on their dosage form, rather than their active ingredient.

Given the absence of authority supporting Ipsen's legal argument, we are left with, and return to, the points of agreement. The parties are fine with the FDA's definition of a protein—"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). The parties agree that the FDA must

determine whether the product's "active ingredient" meets this definition. There is no dispute as to the FDA's definition of "active ingredient"—"any component that is intended to furnish pharmacological activity." 21 C.F.R. § 314.3. Ipsen does not challenge the FDA's scientific judgment that the nanotube structures confer no pharmacological effect. Finally, Ipsen readily acknowledges that Somatuline Depot's active ingredient is lanreotide acetate, an eight amino acid polymer.

Thus, there can be no dispute that lanreotide acetate is not a protein. The District Court correctly granted summary judgment to the FDA and InvaGen.

III.

Ipsen also offers an argument in the alternative: Somatuline Depot is "analogous" to a "protein" and, therefore, qualifies as a biological product. Again, 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. 42 U.S.C. § 262(i)(1).

The FDA has not promulgated a final rule defining "analogous product." Rather, it stakes out the general position that it is inappropriate "to interpret the statutory term 'analogous product' (with reference to a 'protein') in a way that would include amino acid polymers that are specifically excluded by the interpretation of the term 'protein' in the regulation." FDA Brief at 26. Affirmatively, 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." J.A. 480. 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. J.A. 480–81. As an example of a product that is "analogous to a protein," the FDA points to "naturally derived mixtures … 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." J.A. 481. These "naturally derived mixtures" fit the bill, the FDA concludes, because they "*contain* a protein, but are not known to be composed primarily of protein components as their active ingredient." J.A. 481.

We need not search for disagreement on this issue. Ipsen begins with a forceful argument that the FDA's interpretation of "analogous protein" reads "analogous" out of the statute. In its view, the FDA effectively argues that the only products that are "analogous" to proteins are actually proteins. Thus, by concluding that Somatuline Depot is not a protein, it necessarily followed that the FDA would conclude that Somatuline Depot was not analogous to a protein either, Ipsen continues. Such a conclusion is not in accordance with law, Ipsen concludes, because Somatuline Depot "[i]n its finished dosage form—the one that is sold in commerce and administered to patients—the active ingredient lanreotide acetate meets all of the definitional requirements of a protein." Ipsen Brief at 40.

The District Court sided with the FDA. It reasoned that the FDA's interpretation of "analogous" could not have been superfluous even if Ipsen is correct that the FDA's reading "leaves empty the set of products that are analogous to but not actually proteins." *Ipsen II*, 678 F. Supp. 3d at 40. "The statutory term would still include those products that the FDA has explicitly defined as analogous to a virus, therapeutic

serum, toxin, or antitoxin," the District Court further explained. *Id.*; *see also id.* at 41 (referencing *United States v. Turkette*, 452 U.S. 576, 583 n.5 (1981) ("Language in a statute is not rendered superfluous merely because in some contexts that language may not be pertinent.")). But "[i]n any event," the District Court held that the FDA's interpretation did not render "analogous" superfluous even with respect to proteins. *Id.* at 41. That is because the FDA identified "drugs with active ingredients that are comprised of certain naturally derived mixtures that include one or more protein(s) as well as one or more non-biological product component(s) (e.g., lipids)" as analogous to proteins. *Id.* (internal quotation marks omitted).

We agree with Ipsen that "analogous product" includes "analogous proteins." "[T]he natural construction of the language demands that [or analogous product] be read as applicable" to the listed examples that precede it. *Paroline v. United States*, 572 U.S. 434, 447 (2014); *see also Teva Pharmaceuticals USA, Inc. v. FDA*, 514 F. Supp. 3d 66, 115 (D.D.C. 2020) ("The '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."). Here, "or analogous product" immediately follows "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, [and] protein," 42 U.S.C. § 262(i)(1), it therefore follows that any product analogous to these terms is a biologic.

Because Ipsen is correct that "analogous products" include "analogous proteins," we must consider its argument that the FDA's application of "analogous protein" to Somatuline Depot is contrary to law. Ipsen's general point is that a product is "analogous" to a protein even if it has less than forty amino acids, so long as it is "an alpha amino acid polymer with a

specific, defined sequence and is composed of multiple amino acid chains." Ipsen Brief at 40. The FDA's refusal to apply its definition of analogous protein to Somatuline Depot, Ipsen argues, was not in accordance with law. We disagree.

First, the FDA did not read "analogous" out of the statute. It specifically provided an example of a product that was analogous to a protein—a "naturally derived mixture[]" that "contain[s] a protein" even though its active ingredient is composed of more than "protein components." J.A. 481 (emphasis removed). Ipsen's rebuttal that this mixture is a protein is unfairly reductive—quite simply, this mixture is a mixture. Some of the active ingredient's components are proteins, but others are not.

Ipsen's criticism of the FDA's explanation that a product that is "analogous" to a protein must share its "critical characteristics" is similarly reductive. 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.

Second, Ipsen's argument ultimately results in the violation of a "basic principle of administrative law," "courts must be careful not to unduly second-guess an agency's scientific judgments." *Cytori Therapeutics, Inc.*, 715 F.3d at 923. "As we have said, we review scientific judgments of the agency not as the chemist, biologist, or statistician that we are qualified neither by training nor experience to be, but as a reviewing court exercising our narrowly defined duty of holding agencies to certain minimal standards of rationality." *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) (cleaned up). But Ipsen has not shown that the FDA acted unreasonably or arbitrarily and capriciously in concluding that Somatuline Depot was not analogous to a protein.

Let's follow Ipsen's lead: an "analogous protein" includes products that have less than forty amino acids so long as the product is an alpha amino acid polymer with a specific, defined sequence and is composed of multiple amino acid chains.

Not so. The FDA applies "analogous product" narrowly as to proteins because there is a "lack of a precise-agreed upon definition of 'protein.'" J.A. 480. And as already stated, the FDA has decided not to promulgate a rule defining an analogous protein and, instead, will make case-by-case determinations that "leave[] open the possibility that other substances that [it] has not considered and directly addressed could be analogous to a protein even if they are not themselves proteins." FDA Brief at 28. These were, at least in part, scientific judgments. Notably, Ipsen does not argue the FDA's decision or approach conflicts with the ordinary meaning of analogous.

Ipsen further argues that Somatuline Depot is analogous to a protein because "the active ingredient lanreotide acetate meets all of the definitional requirements of a protein" when it is in "its finished dosage form—the one that is sold in commerce and administered to patients." Ipsen Brief at 40.

Once again, we find the FDA rejected Ipsen's arguments based on its scientific expertise. The FDA considered whether the lanreotide nanotube assembly has structural and functional characteristics that are "generally associated with proteins." J.A. 479–80. It ultimately concluded that the lanreotide nanotube assembly fails on both fronts. *Id.* And the FDA further explained that "the lanreotide nanotube assembly does not have a specific biological function that is linked to its structure." J.A. 480. Ipsen does not argue that these conclusions are not supported by substantial evidence or are otherwise arbitrary and capricious. For the foregoing reasons,

we affirm the District Court's grant of summary judgment to the FDA and InvaGen on this front.

So ordered.