Ipsen Biopharmaceuticals, Inc. v. Becerra, 108 F.4th 836 (D.C. Cir. 2024)

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I. WHY IT MADE THE LIST

Disagreement about how law and regulation define certain foundational categories in FDA regulatory law springs eternal. The legislature, FDA, and regulated industry have grappled with the meanings of categories like food, drugs, and biological products for as long as food, drugs, and biological products have been the subject of law and regulation. The D.C. Circuit's 2024 opinion in *Ipsen Biopharmaceuticals, Inc. v. Becerra*, 108 F.4th 836 (D.C. Cir. 2024) is a recent participant in this distinguished tradition. In *Ipsen*, the D.C. Circuit upheld FDA's determination that a depot form of octapeptide lanreotide acetate is a drug (and not a biological product).

In the first instance, how FDA classifies a therapeutic product undoubtedly has material consequences for a product sponsor—it dictates the appropriate regulatory regime, including the approval standards applied by FDA and the lead Center at the agency responsible for reviewing the application. How FDA classifies a product also dictates the available framework for generic or follow-on products and whether, and for how long, any periods of data or market exclusivity apply.

In addition, the *Ipsen* case finds itself squarely within the pitched controversy surrounding the appropriate amount of deference, if any, that courts should give agency action. *Ipsen* was decided within two weeks after the Supreme Court issued its opinion in *Loper Bright v. Raimondo*, 603 U.S. 369 (2024). While any mention of *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984) was meticulously avoided in *Ipsen* and any mention of *Loper Bright* was conspicuously absent, the presence of both cases is strongly felt. So much so that Justice Kagan's dissent in *Loper Bright* specifically cited another dispute about FDA's interpretation of "protein" to question whether eliminating deference was the best allocation of resources.[1]

The *Ipsen* case also confirms that the rough concept of deference to technical agency judgments may live on post-*Loper Bright*. In *Loper Bright* itself, Justice Roberts tiptoed around the idea that "attention" to an agency's judgment may "help inform" a court that is reviewing agency action.[2] Going just a little bit farther, *Ipsen* tipped its cap to the D.C. Circuit's own law, observing that it was a "basic principle of administrative law" that courts "must be careful not to unduly second-guess an

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[1] Loper Bright v. Raimondo, 603 U.S. 369, 456 (2024) (Kagan, J. dissenting) (citing Teva Pharms. USA, Inc. v. FDA, 514 F. Supp. 3d 66, 79–80, 93–106 (D.D.C. 2020)).

[2] *Id.* at 412–13.

agency's scientific judgments."[3] Now, with the next definitional controversy on the horizon, in Eli Lilly's suit against FDA,[4] it is reasonable to ask whether the next generation of cases will look to *Ipsen* to defend agency action.

II. DISCUSSION

A. Legal Background

The Federal Food, Drug, and Cosmetic Act (FDCA) and the Public Health Service Act (PHSA) govern the requirements for introducing drug products and biological products into interstate commerce, respectively. Whether the FDCA or PHSA and all their attendant requirements apply depends on whether an article satisfies the FDCA's definition of "drug" or the PHSA's definition of "biological product."

For drugs, the FDCA prohibits the introduction of a "new drug" into interstate commerce unless FDA approves an application to market such a drug under a New Drug Application (NDA) under 21 U.S.C. § 355(b) or under an Abbreviated New Drug Application (ANDA) under 21 U.S.C. § 355(j). FDA will approve an NDA if it finds that the drug is safe and effective for its intended uses based on "full reports" of investigations showing that a drug is safe and effective. An ANDA need not contain such full reports provided that the ANDA meets the requirements of "sameness" and therapeutic equivalence to a previously approved drug. The Hatch-Waxman Amendments to the FDCA also provided innovators with several periods of exclusivity (e.g., a five-year new chemical entity exclusivity) as well as detailed patent litigation mechanisms.

The PHSA runs an analogous path for biological products. For a biologic, the PHSA prohibits sale in interstate commerce unless FDA approves a Biologics License Application (BLA) under 42 U.S.C. § 262(a) or an Abbreviated Biologics License Application (ABLA) under 42 U.S.C. § 262(k). To earn BLA approval, a sponsor must demonstrate that the biological product is "safe, pure, and potent" or that an ABLA product is "highly similar" to a reference product (i.e., it is a "biosimilar"). When the Biologics Price Competition and Innovation Act (BPCIA) established the biosimilar pathway, the PHSA was amended to provide a twelve-year period of reference product exclusivity and its own detailed patent litigation mechanism.

Whether the FDCA or PHSA applies depends on whether an article meets the statutory definition of "drug" in the FDCA or "biological product" in the PHSA. The FDCA broadly defines a drug as: (A) articles recognized in certain compendial articles; (B) "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals;" (C) "articles (other than food) intended to affect the structure or any function of the body of man or other animals," and (D) components thereof.[5] By contrast, the PHSA defines a "biological product" 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

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[3] *Ipsen*, 108 F.4th 836 at 845–46 (citing Cytori Therapeutics, Inc. v. FDA, 715 F.3d 922, 923 (D.C. Cir. 2013)).

[4] Eli Lilly v. Kennedy, No. 1:24-cv-1503 (S.D. Ind. 2024).

[5] 21 U.S.C. § 321(g)(1).

prevention, treatment, or cure of a disease or condition of human beings."[6] In turn, regulation defines "protein" as "any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size."[7]

The question of whether a product should be regulated as a drug or as something else is certainly not a new one. *United States v. Bacto-Unidisk*, 394 U.S. 784 (1969) is a prominent example of a "definitional controversy," which shows the enduring difficulty presented by the classification of therapeutic products. In this oft-anthologized case, the Supreme Court reversed the lower court determinations that certain antibiotic sensitivity discs were not drugs.[8] The discs in the *Bacto-Unidisk* were round paper discs impregnated with a specific antibiotic intended for placement in contact with a patient specimen culture to assist doctors in the choice of the most effective antibiotic to treat a particular infection.[9] It was undisputed that each disc was used "in laboratory work exclusively . . . ."[10] Rejecting arguments that such use was too indirect to satisfy the definition of "drug," the Supreme Court found it was "plain that Congress intended to define 'drug' far more broadly than does the medical profession."[11]

More recently, the District Court for the District of Columbia addressed whether Teva's Copaxone (glatiramer acetate) product was a drug under the FDCA or a biologic under the PHSA.[12] Glatiramer acetate is a chemically synthesized mixture of peptide copolymers having four specific amino acids in a defined molar ratio but no specific, predetermined sequence.[13] Because the regulatory definition of "protein" requires a "specific, defined sequence," FDA found that glatiramer acetate was not a protein, and hence was not a "biological product" regulated under the PHSA.[14] Teva disagreed, alleging that FDA's determination was inconsistent with other previous determinations classifying allegedly less-defined products as biologics. As another alleged inconsistency, Teva also pointed to FDA's determination that glatiramer acetate was sufficiently well-defined to approve generic drugs.[15]

The D.C. District Court rejected Teva's challenges.[16] In *Teva*, the District Court applied the two-step *Chevron* framework. Thus, the court first analyzed whether Congress directly addressed the precise question at issue and then, as a second step, analyzed whether the agency's interpretation was based on a permissible construction of the statute if it was silent or ambiguous. Judge Howell applied the first step of *Chevron* to find that "[t]he term 'protein' is thus ambiguous with respect to the

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6 42 U.S.C. § 262(i)(1).

7 21 C.F.R. 600.3(h)(6).

8 United States v. Bacto-Unidisk, 394 U.S. 784, 785 (1969).

9 *Bacto-Unidisk*, 394 U.S. at 787.

10 *Id.*

11 *Id.* at 793.

12 Teva Pharms. USA, Inc. v. FDA, 514 F. Supp. 3d 66 (D.D.C. 2020).

13 *Id.* at 81.

14 *Id.*

15 *Id.* at 84. In addition, Teva argued that FDA inconsistently applied the category of product "analogous" to proteins contemplated in the definition of protein. *Id.* at 93–94. Judge Howell also found reasonable that FDA's interpretation of "analogous" product to exclude proteins that otherwise failed to satisfy the requirement of defined sequences.

16 *Id.* at 74.

'specific, defined sequence' requirement, which is neither compelled nor foreclosed by the text of section 351."[17] Then, at the second step, Judge Howell determined that the "specific, defined sequence" requirement of "protein" was "neither unattainable nor, on its face, unduly burdensome for chemically synthesized molecules."[18]

Then, less than two weeks before *Ipsen* was decided, the Supreme Court issued *Loper Bright*. In a decision that will surely inspire voluminous commentary in the years to come, the Court in *Loper Bright* overruled *Chevron*, holding that the deference owed to agency action by *Chevron* "cannot be squared with the APA."[19] Rather, Justice Roberts, speaking for a fractured Court, wrote that "[c]ourts must exercise their independent judgment in deciding whether an agency has acted within its statutory authority."[20] While the majority opinion acknowledged that "attention" to an agency's judgment may "help inform" a court reviewing agency action, it also made clear that courts may not defer to agency interpretation "simply because a statute is ambiguous."

In her dissent, Justice Kagan pressed the "scientific or technical subject matter" of some interpretative issues.[21] Justice Kagan then turned the issue concrete, citing the facts from caselaw of several "typical" *Chevron* problems, including the question addressed by the court in *Teva* ("[w]hen does an alpha amino acid polymer qualify as such a 'protein'?").[22] Justice Kagan's soliloquy about proteins is notable:

> Consider, for example, the first bulleted case above. When does an alpha amino acid polymer qualify as a "protein"? I don't know many judges who would feel confident resolving that issue. (First question: What even *is* an alpha amino acid polymer?) But the FDA likely has scores of scientists on staff who can think intelligently about it, maybe collaborate with each other on its finer points, and arrive at a sensible answer.[23]

Based on this example, among others, Justice Kagan argued that "agencies often know things about a statute's subject matter that courts could not hope to"—especially when the statute is of a "scientific or technical nature."[24]

B. Factual Background

FDA approved Somatuline Depot (lanreotide acetate) solution for subcutaneous administration in August 2007 as a drug under NDA No. 22-074.[25] The active ingredient in Somatuline Depot, lanreotide acetate, is a synthetic octapeptide analog of the natural hormone, somatostatin.[26] In Somatuline Depot, lanreotide acetate assembles into nanotube structures, which facilitate diffusion of lanreotide acetate.[27]

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[17] *Id.* at 102.

[18] *Id.* at 106.

[19] *Loper Bright*, 603 U.S. at 396.

[20] *Id.* at 412.

[21] *Id.* at 449 (Kagan J, dissenting).

[22] *Id.* at 452.

[23] *Id.* at 456 (emphasis in original) (internal citation omitted).

[24] *Id.*

[25] Somatuline Depot Label at 1 (Aug. 30, 2007).

[26] *Id.* at 10.

[27] Ipsen Biopharmaceuticals, Inc. v. Becerra, 108 F.4th 836 (D.C. Cir. 2024).

When Somatuline Depot was initially approved in 2007, it was protected by a five-year new chemical entity exclusivity, a seven-year orphan drug exclusivity, and a patent expiring in 2015.[28]

When FDA left Somatuline Depot off a list of NDAs transitioned to BLAs, Ipsen asked FDA to reconsider.[29] FDA stood by its decision and Ipsen sued FDA.[30] The district court dismissed Ipsen's complaint because it found Ipsen lacked standing. Specifically, the district court found that Ipsen's fears were too speculative—to show standing, Ipsen would need to show that a generic applicant would file an ANDA referencing Somatuline Depot, that FDA would approve that ANDA, and that the hypothetical ANDA product would fail to satisfy the standard of similarity established by the PHSA for follow-on biological products.[31]

But Ipsen's fears soon grew less speculative. Shortly thereafter, FDA approved an ANDA submitted by Invagen to market a generic version of Somatuline Depot, and Ipsen sued FDA once again.[32] Ipsen argued that, when assembled into the nanotube structures, lanreotide acetate would have over forty amino acids and therefore would meet the regulatory definition of protein.[33] Alternatively, Ipsen argued that the nanotube assembly satisfied the definition of "biological product" as "an analogous product" to a protein. Ipsen concluded that FDA's determination violated the APA because it was arbitrary and capricious or otherwise not in accordance with law.[34]

The D.C. District Court granted summary judgment in favor of FDA and the intervenor Invagen.[35] First, the District Court rejected Ipsen's legal challenge to FDA's decision to consider the length of lanreotide acetate "standing alone" rather than altogether in the final drug product, finding FDA's decision to analyze the length of peptides in terms of "just" lanreotide acetate and not the nanotubes, "unambiguously correct."[36] The District Court also rejected Ipsen's disagreement with FDA's scientific judgment that stand-alone lanreotide acetate was the active ingredient, finding that FDA's determination was "rational, carefully explained, and consistent with the record evidence."[37] Moreover, the District Court rejected Ipsen's argument that FDA erred in not accepting Somatuline Depot as a product "analogous" to a protein.[38] Ipsen appealed.

C. Decision

The D.C. Circuit affirmed the District Court's resolution of the summary judgment motions in favor of FDA and against Ipsen. Writing for the panel, Judge Wilkins

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[28] U.S. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, PATENT AND EXCLUSIVITY INFORMATION ADDENDUM ADA 77 (28th ed. 2008).

[29] *Ipsen*, 108 F.4th at 839.

[30] Ipsen Biopharmaceuticals, Inc. v. Becerra, 2021 U.S. Dist. LEXIS 183825 (D.D.C. 2021).

[31] *Ipsen*, 2021 U.S. Dist. LEXIS 183825, at 13–14.

[32] *See Ipsen*, 108 F.4th at 840.

[33] *Id.*

[34] *Id.*

[35] Ipsen Biopharmaceuticals, Inc. v. Becerra, 678 F. Supp. 3d 20 (D.D.C. 2023).

[36] *Id.* at 36–37.

[37] *Id.* at 39.

[38] *Id.* at 39–40.

surveyed the significant points of agreement between the parties. For example, the court noted that parties "largely agree on the law"—notably, Ipsen did not challenge the propriety of the regulatory definition of protein (i.e., "any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size").[39] The court also noted "broad agreement on how the law applies to the facts"—that lanreotide acetate consists of eight peptides, that it assembles into nanotubes of greater than 40 amino acids in the finished dosage form, and that the nanotubes do not provide any pharmacological effect.[40]

The court framed the dispute, then, in terms of a disagreement about whether the statutory definition of "biological product" incorporates the regulatory definition of "drug product" (which in turn is defined as a "finished dosage form.")[41] But the court determined that, "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."[42] In practice, the court observed that following Ipsen's argument to its logical conclusion would lead to a "killer contradiction"—that Somatuline Depot would qualify as a biological product, but that other immediate release lanreotide acetate products would not (e.g., products that did not assemble into nanotubes).[43]

The D.C. Circuit also rejected Ipsen's argument that "biological products" are "merely types of drug products" and therefore the finished dosage form requirement of "drug product" should apply to biological products. The court still found, however, that the conclusion was not compelled by the premise, stating that, "[b]ut even so, that does not mean Congress silently incorporated the FDA's definition of a 'drug product' into the definition of a 'biological product.'"[44]

The court also rejected Ipsen's argument that Somatuline Depot qualifies as a biological product because it is "analogous" to a protein. While FDA has not promulgated a final rule on the meaning of "analogous product" in the statutory definition, the court observed that FDA "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.'"[45] More positively, FDA states that "analogous" products "must share the critical characteristics of the relevant category of biological product," such as the number of amino acid residues and the requirement for a specific, defined sequence.[46] As an example, FDA offered naturally derived mixtures including a protein and one or more non-biological product components such as a lipid where the mixture is not primarily comprised of protein.[47]

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[39] *Ipsen*, 108 F.4th at 841.

[40] *Id.*

[41] *Id.* (citing the definition of drug product in 21 C.F.R. § 314.3(b)).

[42] *Id.* at 843.

[43] *Id.*

[44] *Id.* at 843–44.

[45] *Id.* at 844 (citing FDA's Brief at 26).

[46] *Id.*

[47] *Id.*

Ipsen argued that FDA's interpretation of "analogous product" reads the word "analogous" out of the definition.[48] The D.C. Circuit disagreed.[49] The court observed that FDA identified an example of an analogous product that shared a protein's "critical characteristics, while also having other distinguishable characteristics" (e.g., a protein-lipid mixture described above).[50] Notably, the D.C. Circuit still cited its own law in *Cytori Therapeutics, Inc. v. FDA*, 715 F.3d 922 at 923 (D.C. Cir. 2013) for the "basic principle of administrative law" that courts "must be careful not to unduly second-guess an agency's scientific judgments."[51] On this point, the court found that Ipsen failed to show that FDA's scientific judgments were not supported by substantial evidence or that FDA acted arbitrarily and capriciously in their determination.[52] Thus, the D.C. Circuit affirmed.

IMPACT OF THE DECISION

Ipsen v. Becerra is certainly not the first "definitional controversy" relating to the fundamental categories of FDA regulatory law. Each time that controversy arises about a core concept of FDA regulatory law (e.g., food, drugs, or biological products), opportunities arise to learn more about how scientists and industry use the term, its legal definition, the touchpoints between the two, and the process that agencies use to mediate both and achieve policy goals.

In addition, the *Ipsen* case presents additional clarification on the meaning of the term "analogous products" in the statutory definition of "biological product." Before *Ipsen*, the D.C. District Court in *Teva Pharms. USA, Inc. v. United States FDA*, 514 F. Supp. 3d 66 (D.D.C. 2020) had already ratified FDA's position that "analogous product" cannot include peptides lacking a "specific, defined sequence." Then, in the *Ipsen* case, the D.C. Circuit ratified several refinements, including that "analogous products" cannot include peptides containing fewer than 40 amino acids. Taking *Teva* and *Ipsen* together, these cases suggest that an "analogous product" cannot include features that would vitiate the meaning of any other subclass of "biological product."

Ipsen v. Becerra will not be the last "definitional controversy." In fact, another dispute is presently before the District Court for the Southern District of Indiana about whether FDA properly classified a 41-peptide investigational product, retatrutide, as a drug versus a biological product.[53] And this time, with *Chevron* overruled, retatrutide's sponsor Eli Lilly forcefully argues that any scientific or technical judgment used by FDA should be afforded *no* deference. But query whether the notion of deference to agency scientific judgment will abide notwithstanding *Loper Bright*—whether a less structured concept exists independently from *Chevron*, and therefore will continue to exist after *Chevron*. In its summary judgment briefing in the *Eli Lilly* case, FDA pointed to *Ipsen* as "noting, post-*Loper Bright*, that courts must still "be careful not to

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[48] *Id.* at 844–45.

[49] *Id.* at 845–46.

[50] *Id.* at 845.

[51] *Id.* at 846.

[52] *Id.*

[53] Eli Lilly v. Kennedy, No. 1:24-cv-1503 (S.D. In. 2024). Because even though retatrutide consists of greater than forty amino acids, it does not contain greater than forty *alpha* amino acids.

unduly second-guess [FDA's] scientific judgements."[54] The most enduring aspect of the *Ipsen* case may very well be this proposition.

[54] Defendants' Memorandum in Support of their Cross-Motion for Summary Judgment and Opposition to Plaintiff's Motion for Summary Judgment at 16 n.7, Eli Lilly v. Kennedy, No. 1:24-cv-1503 (S.D. In. 2024).