UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

TEVA PHARMACEUTICALS USA, INC., *et al.*, Plaintiffs, v. UNITED STATES FOOD AND DRUG ADMINISTRATION, *et al.*, Defendants, *and* SANDOZ INC., *et al.*, Intervenor-Defendants.	Civil Action No. 20-808 (BAH) Chief Judge Beryl A. Howell

MEMORANDUM OPINION

Plaintiffs Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. (together, "Teva") and intervenor-defendants Sandoz Inc. ("Sandoz") and Mylan Pharmaceuticals Inc. ("Mylan") are pharmaceutical companies that manufacture therapeutic products using glatiramer acetate to treat relapsing-remitting forms of multiple sclerosis. Almost 25 years ago, in 1996, the Food and Drug Administration ("FDA") approved Teva's glatiramer acetate product, Copaxone, as a drug under the Food, Drug, and Cosmetics Act ("FDCA"), 21 U.S.C. § 301 *et seq*. Years later, and in the face of concerted resistance by Teva, the agency approved generic glatiramer acetate products, including those manufactured by Sandoz and Mylan. Now, in yet another effort to stifle Copaxone competitors, Teva brings this lawsuit, seeking an order compelling FDA to regulate Copaxone as a "biological product" under the Public Health Service Act ("PHSA"), 42 U.S.C. § 201 *et seq.*, rather than as a "drug" under the

FDCA. According to Teva, such a change was mandated by the Biologics Price Competition and Innovation Act of 2009 ("BPCIA"), Pub. L. No. 111-148, tit. VII, subtit. A, 124 Stat. 119, 804–21 (2010), and subsequent amendments, which expanded the definition of "biological product" to include "proteins" and therapeutic products "analogous" to proteins and required FDA to transition qualifying drugs to biological product status by March 23, 2020.

Teva instituted this action on March 24, 2020 against FDA and the Department of Health and Human Services, as well as the heads of those agencies in their official capacities (together, the "federal defendants"), challenging FDA's determination that Copaxone is neither a protein nor a product analogous to a protein and therefore cannot be transitioned from the FDCA to the PHSA. *See generally* Compl., ECF No. 1. Shortly after, Mylan and Sandoz intervened as defendants. Mot. Intervene by Sandoz Inc., ECF No. 9; Mot. Intervene as Def., ECF No. 19; Min. Order (Apr. 20, 2020) (granting Sandoz's motion to intervene); Min. Order (Apr. 27, 2020) (granting Mylan's motion to intervene).

Now pending before the Court are cross-motions for summary judgment filed by Teva, ECF No. 31, the federal defendants, ECF No. 36, Mylan, ECF No. 34, and Sandoz, ECF No. 38. For the reasons explained below, Teva's motion is denied and the motions of the federal defendants and the intervenor-defendants are granted.

I. BACKGROUND

A. Statutory and Regulatory Background

FDA administers two statutory frameworks for the regulation and approval of two distinct categories of therapeutic products. The FDCA's section 505 governs the approval of new "drugs," 21 U.S.C. § 355, while the PHSA's section 351 governs the approval of new biological products or biologics, 42 U.S.C. § 262. "A biologic is a type of drug derived from natural, biological sources such as animals or microoorganisms," in contrast to "traditional

drugs, which are typically synthesized from chemicals." *Sandoz Inc. v. Amgen Inc.* ("*Sandoz*"), 137 S. Ct. 1664, 1669–70 (2017). Both drugs and biological products are used to treat and prevent disease in the human body. *See* 21 U.S.C. § 321(g)(1)(B)–(C) (defining a "drug" as an "article[] intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease" or "intended to affect the structure or any function of the body of man"); 42 U.S.C. § 262(i)(1) (stating that a "biological product" must be "applicable to the prevention, treatment, or cure of a disease or condition of human beings").

1. Approval of Drugs Under the FDCA

The FDCA controls the approval of "drugs" by FDA through any of three pathways available under section 505. First, an applicant may file a new drug application ("NDA") containing scientific data collected by the applicant, 21 U.S.C. § 355(a), (b)(1), which demonstrates that the drug is safe and effective for use as labeled, *id.* § 355(d). Second, an applicant may file an NDA relying on scientific investigations "not conducted by or for the applicant and for which the applicant has not obtained a right or reference or use" to show safety and efficacy, if accompanied by additional information specified in the statute. *Id.* § 355(b)(2). Drugs approved through either of these pathways are commonly referred to as "brand-name" drugs.

Finally, an applicant may file an abbreviated new drug application ("ANDA") to bring a generic version of a previously approved brand-name drug (the "reference listed drug") to market. *Id.* § 355(j). An ANDA relies on FDA's previous finding that the reference listed drug is safe and effective. Thus, to gain approval for an ANDA, an applicant must show that the proposed generic drug is "the same as" the reference listed drug, *id.* § 355(j)(2)(A) (ii), (iii), a standard that requires the generic drug to be "identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use," 21 C.F.R. § 314.92(a)(1). The applicant

must also establish that the proposed generic is "bioequivalent to" the reference listed drug, meaning that the generic drug "can be expected to have the same therapeutic effect" as the reference listed drug. 21 U.S.C. § 355(j)(2)(A)(iv). FDA makes active-ingredient-sameness determinations for ANDAs "on a case-by-case basis." Admin. Record ("AR") at 728.[1]

As part of the NDA process, applicants seeking FDA approval must provide information about "any patent which claims the drug" that is the subject of the NDA "or which claims a method of using" the drug "with respect to which a claim of patent infringement could reasonably be asserted." 21 U.S.C. § 355(b)(1), (2)(A), (c)(2). The FDA lists all such patents in a publication entitled *Approved Drug Products with Therapeutic Equivalence Evaluations* and commonly known as the "Orange Book." *See id.* § 355(j)(7); FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations* iv–xi (40th ed. 2020), https://www.fda.gov/media/71474/download. "Process patents" (that is, patents claiming methods of manufacturing or producing a drug) are not among the patents provided during the NDA process and therefore are not included in the Orange Book. *See* 21 C.F.R. § 314.53(b)(1).

If an ANDA applicant seeks to market a generic version of a brand-name drug before a related patent in the Orange Book has expired, the ANDA applicant must file a "Paragraph IV certification," certifying that the unexpired patent "is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the [ANDA] is submitted." 21 U.S.C. § 355(j)(2)(A)(vii)(IV); *see also Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676–77 (1990).

[1] FDA submitted a certified list of the contents of the administrative record, in accordance with Local Civil Rule 7(n)(1), *see* Index of Admin. Record, ECF No. 29; Index of Suppl. Admin. Record, ECF No. 33, and, as agreed by the parties and approved by the Court, *see* Joint Mot. Entry of Scheduling Order at 3, ECF No. 32; Min. Order (June 22, 2020), also submitted the entire administrative record, totaling 1151 pages and including documents dating from 1995 to 2020, *see* ECF No. 42-1 (AR at 1–278); ECF No. 42-2 (AR at 279–555); ECF No. 42-3 (AR at 556–1132); ECF No. 42-4 (AR at 1133–51). Consistent with Local Civil Rule 7(n)(1), the portions of the administrative record cited or otherwise relied upon in the parties' briefing have been separately docketed. *See* J.A., ECF No. 46. For clarity, "AR" citations are to the full administrative record, rather than to the joint appendix.

The ANDA applicant must also provide notice of the Paragraph IV certification, setting forth "a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed," to both the patent holder and the NDA holder. 21 U.S.C. § 355(j)(2)(B)(iv)(II). The filing of a Paragraph IV certification is deemed "an [artificial] act of infringement," sufficient to form the basis of a patent infringement action, if the purpose of the certification "is to obtain approval under" the FDCA "to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent." 35 U.S.C. § 271(e)(2). The NDA or patent holder may therefore bring a patent infringement suit based on the Paragraph IV certification alone. *See id.* § 271(a)–(c), (e)(2); *Eli Lilly & Co.*, 496 U.S. at 678; *Caraco Pharm. Lab'ys., Ltd. v. Forest Lab'ys., Inc.*, 527 F.3d 1278, 1283 (Fed. Cir. 2008). In contrast, the potential infringement of a process patent does not require a Paragraph IV certification and thus does not trigger a patent holder's right to bring a preapproval infringement suit.

2. Approval of Biological Products Under the PHSA

Section 351 of the PHSA, as amended by the BPCIA, provides two avenues to FDA approval of biologics. First, applicants seeking to bring a new biological product to market must submit a biologics license application ("BLA") for FDA approval. 42 U.S.C. § 262(a). FDA may license a new biologic if, among other criteria, the manufacturer shows that the product is "safe, pure, and potent." *Id.* § 262(a)(2)(C)(i)(I).

Second, the PHSA provides an abbreviated pathway to approval, created by the BPCIA, for "biosimilars," which are "biologic product[s] that [are] highly similar to a biologic product that has already been approved by the [FDA]." *Sandoz*, 137 S. Ct. at 1669. An applicant seeking approval of a biosimilar must submit an abbreviated biologics license ("aBLA"). 42 U.S.C. § 262(k). An aBLA need not replicate the "safe, pure, and potent" showing made in the

BLA for the previously approved biologic product (the "reference product"). *See id.* § 262(k)(2)(A)(iii). Instead, an aBLA applicant must show that its product is "highly similar" to the previously approved biologic product (the "reference product") and that "no clinically meaningful differences" with respect to "safety, purity, and potency" exist between the two products. 42 U.S.C. § 262(i)(2)(A), (B); *see also id.* § 262(k)(2)(A)(i)(I).

The BPCIA's amendments to the PHSA "establish[] processes both for obtaining FDA approval of biosimilars and for resolving patent disputes between manufacturers of licensed biologics and manufacturers of biosimilars." *Sandoz*, 137 S. Ct. at 1669. As soon as the initial approval process for a biosimilar is underway, the patent dispute process commences. FDA notifies an aBLA applicant when its application has been accepted for review, triggering a twenty-day period during which the applicant "shall provide" a copy of the aBLA and information about how the biosimilar is made to the manufacturer of the reference product (the "sponsor"), 42 U.S.C. § 262(l)(2)(A), and "may provide" additional information requested by the sponsor, *id.* § 262(l)(2)(B). This notice requirement "enable[s] the sponsor to evaluate the biosimilar for possible infringement of patents it holds on" the underlying biologic, *Sandoz*, 137 S. Ct. at 1670–71, and initiates the so-called "patent dance," an optional process in which "the parties exchange information to identify relevant patents and to flesh out the legal arguments that they might raise in future litigation," *id.* at 1671.

At the close of the patent dance, the BPCIA allows the parties immediately to litigate any disputed patents included on a list developed by the parties through negotiation or, failing a negotiated agreement, formed through statutory procedures, in an artificial patent infringement action brought by the sponsor. *See* 42 U.S.C. §§ 262(l)(3)–(6); 35 U.S.C. § 271(e)(2)(C); *Sandoz*, 137 S. Ct. at 1671–72. Disputed patents that are not litigated at this phase may be

challenged in a second phase of litigation initiated by the aBLA applicant's notice of commercial marketing, which notice the applicant "shall provide" to the sponsor "not later than 180 days before the date of the first commercial marketing" of the biosimilar. 42 U.S.C. § 262(l)(8)(A). "In this second phase of litigation, either party may sue for declaratory relief," *Sandoz,* 137 S. Ct. at 1672 (emphasis omitted) (citing 42 U.S.C. § 262(l)(9)(A)), and "the sponsor may 'seek a preliminary injunction prohibiting the [biosimilar] applicant from engaging in the commercial manufacture or sale of [the biosimilar]'" while second-phase challenges are pending, *id.* (alterations in original) (quoting 42 U.S.C. § 262(l)(8)(B)).

If an aBLA applicant fails to provide the application and information to the sponsor as required by 42 U.S.C. § 262(l)(2)(A), thereby dodging the patent dance entirely, the sponsor may immediately bring an action "for a declaration of infringement, validity, or enforceability of any patent that claims the biological product or a use of the biological product." 42 U.S.C. § 262(l)(9)(C). "[35 U.S.C. §] 271(e)(2)(C)(ii) facilitates this action by making it an artificial act of infringement, with respect to [such] patent[s] . . . , to submit a biosimilar application." *Sandoz,* 137 S. Ct. at 1672. The declaratory judgment action provided in 42 U.S.C. § 262(l)(9)(C) is the exclusive remedy for an applicant's failure to comply with 42 U.S.C. § 262(l)(2)(A)'s disclosure requirement. *Id.* at 1675.

3. "Proteins" Become "Biological Products"

Until 2010, section 351 of the PHSA defined a "biological product" as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, 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) (2006). In 2010, Congress passed the BPCIA, which expanded the definition of "biological products" to include any "protein (except

any chemically synthesized polypeptide)." BPCIA § 7002(b), 124 Stat. at 814; *see also* 42 U.S.C. § 262(i)(1) (2012). "Biological product" now meant "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, *protein (except any chemically synthesized polypeptide),* 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) (2012) (emphasis added). Congress did not define key terms in the 2010 amendment, including "protein," "chemically synthesized," or "polypeptide." The BPCIA further provided that NDAs or ANDAs for any products previously approved as drugs under the FDCA that now qualified as "biological products" under the revised definition would be transitioned to BLAs or aBLAs under the PHSA by March 23, 2020. BPCIA § 7002(e)(4), 124 Stat. at 817 (codified at 42 U.S.C. § 262 note).

In late 2019, Congress again revisited the definition of "biological products" and removed the parenthetical exception for chemically synthesized polypeptides. *See* Further Consolidated Appropriations Act, 2020, Pub. L. No. 116-94, § 605, 133 Stat. 2534, 3127 (2019) ("2019 Act"). Section 351 in its current form thus defines "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 prevention, treatment, or cure of a disease or condition of human beings," 42 U.S.C. § 262(i)(1) (emphasis added), and subjects all such products to the PHSA's licensing requirements, *see id.* § 262(a).

4. FDA's Interpretation of "Protein"

Soon after the passage of the BPCIA, FDA began developing regulations to interpret the terms "protein" and "chemically synthesized polypeptide" in the amended definition of

"biological product" and, in turn, to determine which products would be transitioned from "drug" to "biological product" status under the new definition. The FDA's application of these regulations to Teva's Copaxone product in a decision memorandum prompted this lawsuit.

(a) The 2011 Memorandum

On October 5, 2010, FDA requested comments from the pharmaceutical industry as to "[w]hat scientific and technical factors" should be considered in "develop[ing] a regulatory definition" for the terms "protein" and "chemically synthesized polypeptide." AR at 121. The agency also created "a cross-center, multi-disciplinary 'protein definition working group' that conducted an extensive analysis of potential approaches that the agency could take" in interpreting the terms. *Id.* at 293. The working group's deliberations, industry comments, and FDA's resulting conclusions were described in an August 1, 2011 internal memorandum signed by the Directors of FDA's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research ("2011 Memorandum"). *Id.* at 292–310. The 2011 Memorandum explained the "considerable variability in how scientific sources define" the terms "protein," "chemically synthesized," and "polypeptide." *Id.* at 293. Nonetheless, FDA identified scientific consensus as to at least two elements of the definitions.

First, FDA concluded that "proteins," "polypeptides," and "peptides" in scientific literature are all "amino acid polymers," or chains, "made up of alpha amino acids linked by peptide bonds." *Id.* at 297. "Proteins are long, complex polymers of amino acids," *id.*, while peptides are "simpler, shorter amino acid chains" not considered to be proteins, *id.* at 298. This scientific consensus, in combination with the BPCIA's intent to create "a new abbreviated approval pathway [the aBLA process] with statutory criteria better suited" to complex interchangeable products than the "sameness" standard applied to generic drugs under the

FDCA, *id.* at 299, led to the determination that "proteins" within the meaning of the BPCIA should have a minimum size requirement, as a bright-line proxy for complexity, *see id.* at 299–300, 302–04. A forty amino acid cut-off, under which amino acid polymers of fewer than forty amino acids would be treated as peptides rather than proteins, was found to have "significant support in the literature" and to be "consistent" with other FDA regulations concerning peptides. *Id.* at 305.

Second, FDA found that the term "protein," as used in scientific sources, consistently referred to "chains containing a specific, defined sequence of amino acids, generally provided by the DNA [deoxyribose nucleic acid] sequence of a corresponding gene." *Id.* at 297. The 2011 Memorandum cited a variety of scientific references in support of this consensus. *See, e.g.*, *id.* at 295, 295 n.14, 296–97, 297 nn.32–33. Thus, FDA determined that amino acid polymers without a "specific, defined amino acid sequence," for example, "chemically synthesized polymers with random sequences, (e.g., glatiramer)," are not proteins and therefore "are not subject to the parenthetical exclusion [for chemically synthesized polypeptides] in the first place." *Id.* at 307. In reaching this conclusion, FDA acknowledged that the statutory term "protein" included chemically synthesized proteins, *see, e.g.*, *id.* at 306 ("[I]f Congress wished to exclude all chemically synthesized proteins from the definition of biological product, it would have used 'protein' in the parenthetical instead of 'polypeptide.'"), and reviewed scientific articles about the chemical synthesis of proteins, *see, e.g.*, *id.* at 306 nn.60–61.

In its efforts to interpret the parenthetical exclusion—*i.e.*, defining "biological product" as "a . . . protein (except any chemically synthesized polypeptide), or analogous product," 42 U.S.C. § 262(i)(1) (2012)—FDA confronted "[t]he challenge" of the absence of scientific consensus around "a generally accepted meaning" of "polypeptide." *Id.* at 306. The agency thus

sought to craft a definition of "chemically synthesized polypeptide" that "fit[] within the statutory language and ma[de] regulatory sense." *Id.* Looking to the structure of the parenthetical exception, which was designed to exclude a narrower subset of molecules from the broader category of proteins, FDA determined that "chemically synthesized polypeptides" must refer to a smaller group of "molecules that would otherwise fall within the 'protein' term." *Id.* Further, although emerging technologies continue to push the boundaries of chemical synthesis, FDA recognized that "chemical synthesis of amino acid polymers with a defined sequence has historically been restricted to shorter peptide chains," *id.*, providing some indication of the types of molecules Congress might have had in mind when drafting the exception, *id.* at 306–07. FDA next turned to congressional intent, noting that, because the BPCIA meant to create a regulatory regime better tailored to highly complex molecules, excluding certain extremely complicated substances from the definition of "biological product" solely because they are chemically synthesized would contradict the purpose of the law. *See id.* For these reasons, FDA "infer[red] that Congress intended for the parenthetical exclusion to apply only to relatively short, less complex amino acid polymers," and, again using length as a proxy for complexity, determined that polymers of fewer than 100 amino acids in length met this criteria. *Id.* at 307.

As a result of this analysis, the 2011 Memorandum defined "protein" as "any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size" and "chemically synthesized polypeptide" as "any alpha amino acid polymer is that is (a) made entirely by chemical synthesis; and (b) less than 100 amino acids in size." *Id.* at 292 (footnote omitted).

(b) Guidance Documents

On February 15, 2012, FDA announced the availability of a draft guidance document, open to public comment, on the implementation of the BPCIA ("2012 Guidance Document") that, in relevant part, set forth FDA's interpretation of "protein" and "chemically synthesized polypeptide." *Id.* at 311–30.[2] The 2012 Guidance Document adopted the definitions developed in the 2011 Memorandum, stating that "[t]he term 'protein' means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size" and "[t]he term 'chemically synthesized polypeptide means any alpha amino acid polymer that (1) is made entirely by chemical synthesis; and (2) is less than 100 amino acids in size." *Id.* at 328. In establishing the elements of these definitions, FDA relied on the analysis described in the 2011 Memorandum. *See id.* at 311–30. This guidance was finalized, and again made open to public comment, on April 30, 2015 ("2015 Guidance Document"). *See id.* at 740–60. The 2015 Guidance Document provided the same definitions of "protein" and "chemically synthesized polypeptide," *id.* at 758, and again relied on substantially the same analysis, as the 2012 Guidance Document and the 2011 Memorandum, *see id.* at 740–60. A third guidance document, issued on March 14, 2016 ("2016 Guidance Document"), *id.* at 782–95, published the identical definitions again, *id.* at 787 n.3.

(c) 2018 Proposed Rule and 2020 Final Rule

On December 12, 2018, FDA published a notice of proposed rulemaking and a proposed rule to codify its interpretations of "protein" and "chemically synthesized polypeptide" (the "Proposed Rule"). *Id.* at 800–07. The Proposed Rule, like the earlier Guidance Documents, canvassed the scientific literature and detailed the scientific, regulatory, and legal considerations

[2] Teva submitted comments to the 2012 Guidance Document, but did not address FDA's interpretation of the terms "protein" and "chemically synthesized polypeptide." *See* AR at 331–41.

taken into account by the agency (including public comments submitted in response to the 2012 and 2015 Guidance Documents), *id.* at 802–03, and included the agency's previously published definitions of "protein" and "chemically synthesized polypeptide," unaltered from the Guidance Documents, *id.* at 801. FDA again emphasized the scientific consensus at the heart of its interpretation, that the term "protein refers to chains containing a specific, defined sequence of amino acids." *Id.* at 803 (emphasis omitted). The public comment period for the Proposed Rule closed on February 25, 2019. *Id.* at 800.

Nearly ten months later, on December 20, 2019, Congress passed the 2019 Act, removing the parenthetical exception for chemically synthesized polypeptides from the PHSA's definition of "biological product." FDA did not reopen the Proposed Rule for a new round of comments in light of the new law. Instead, on February 21, 2020, two months after the 2019 Act was enacted, FDA published its Final Rule, *id.* at 1024–30, codifying the definition of "protein" set forth in the 2011 Memorandum; the 2012, 2015, and 2016 Guidance Documents; and the Proposed Rule "without change," *id.* at 1025. "[I]n light of the [2019] Act," however, FDA did not "finaliz[e] its interpretation of 'chemically synthesized polypeptide' because it [was] no longer necessary." *Id.* The agency clarified that, "[w]ith the . . . removal of the parenthetical exception . . . all amino acid polymers that meet FDA's interpretation of the term 'protein' (including an amino acid polymer that previously would have fallen within the term 'chemically synthesized polypeptide' as interpreted by FDA) will be considered to fall within the statutory definition of 'biological product.'" *Id.* at 1026. Aside from these statements, made in the context of responding to comments that had been submitted with respect to the Proposed Rule's definition of "chemically synthesized polypeptide," FDA offered no further analysis or explanation of the 2019 Act's impact, if any, on its interpretation of the term "protein."

At no time during its nearly decade-long rulemaking process did FDA provide a regulatory definition for "analogous product" as applied to products "analogous" to proteins. In the Final Rule, FDA observed that "[a] definition of products that are 'analogous' to a 'protein' . . . is outside the scope of this rulemaking," but that "it would not be appropriate for the statutory term 'analogous product' to be interpreted in a way that would include products that are specifically excluded by this final rule." *Id.* at 1028.

B. Approval and Classification of Glatiramer Acetate Products

1. Manufacture and Composition of Copaxone

Copaxone, the therapeutic product at issue in this action, is an injectable used for the "reduction of relapses in patients with relapsing-remitting multiple sclerosis." *Id.* at 3. Its active ingredient, glatiramer acetate, is a chemically synthesized "mixture of peptide copolymers containing four specific amino acids in a defined molar ratio." *Id.* at 706. Glatiramer acetate is synthesized "via amino acid polymerization [] followed by a subsequent cleavage or partial depolymerization step[.]" *Id.* at 706. In the first step, polymerization, the amino acids are assembled into chains, or polymers. *Id.* at 709–13. "[W]hile the addition of . . . amino acids to the copolymer chain is not determined by a pre-determined sequence, it is also not a purely random event." *Id.* at 712. Rather, the sequence of the polymers (that is, the order in which amino acids are added to the chains) is determined by reaction chemistry. The reactivities of the four amino acids in glatiramer acetate differ. As a result, "their corresponding relative rates of incorporation into the copolymer chains" also differ, *id.* at 712, and, in a phenomenon known as "propagational shift," "the molar fractions of each [amino acid] . . . vary across the synthesized chain," *id.* at 713. The degree of variation is predictable, but not certain, based on the relative reactivity of the amino acids: more reactive amino acids tend to appear at the beginning of the chain and less reactive amino acids tend to appear towards the end. *Id.* at 713. This

predictability means that "the chance of producing a conserved local amino acid sequence is increased, which is consistent with the conservation [or replication] of local sequences between batches of Copaxone." *Id.* at 713.

In the second step, partial depolymerization, the copolymer chains formed during polymerization are "cleaved," or broken into smaller pieces, to produce chains within a specified molecular weight distribution characteristic of glatiramer acetate. *Id.* at 714. The amino acid sequences are not changed at this stage. *Id.*

2. NDA and ANDAs for Copaxone and Other Glatiramer Acetate Products

In 1995, Teva submitted an NDA for Copaxone, which FDA approved on December 20, 1996. *Id.* at 3. Since that time, Teva has pursued every available avenue to prevent other glatiramer acetate products from coming to market. *See generally* Staff of H.R. Comm. on Oversight & Reform, 116th Cong., *Rep. on Drug Pricing Investigation: Teva—Copaxone* (2020), https://oversight.house.gov/sites/democrats.oversight.house.gov/files/Teva%20Staff%20Report%2009-30-2020.pdf.

First, Teva has initiated numerous patent suits against its competitors. *See, e.g.*, Mylan's Combined Mem. Supp. Mylan's Cross-Mot. Summ. J. & Resp. Pls.' Mot. Summ. J. ("Mylan Mem.") at 2, ECF No. 34-1 (describing Teva's "near decade-long patent battle in the courts, filing almost a dozen patent litigations against Mylan, Sandoz, and others"); Sandoz Inc.'s Consolidated Mem. Opp'n Pls.' Mot. Summ. J. & Supp. Sandoz Inc.'s Cross-Mot. Summ. J. ("Sandoz Mem.") at 1, ECF No. 38-1 ("Teva has . . . pursu[ed] multiple lawsuits to tie up Sandoz, Mylan and other competitors in the courts."). Relevant to this litigation, at present, Teva holds two patents "claim[ing] processes for manufacturing glatiramer acetate by filtering under specified temperature conditions," U.S. Patent Nos. 9,155,755 ("'775 Patent") and 9,763,993

("'993 Patent"), and "at least one patent . . . claiming methods of treatment using" Copaxone, U.S. Patent No. 9,402,874 ("'874 Patent"). Decl. of Colman Ragan ¶ 6 ("Ragan Decl."), ECF No. 40-1. The '775 and '993 Patents, as process patents, were never listed in the Orange Book; the '874 Patent was listed in the Orange Book until this year, "when Teva requested its removal following court decisions on other patents directed to methods of using" Copaxone. *Id.*

Second, as part of this campaign, from 2008–2015, Teva filed eight Citizen Petitions with FDA, seeking to block the approval of ANDAs for generic glatiramer acetate products, all of which were denied. *See* AR at 19–52 (Sept. 26, 2008 Citizen Petition), 69–106 (Nov. 13, 2009 Citizen Petition), 171–99 (Dec. 10, 2010 Citizen Petition), 342–76 (June 4, 2012 Citizen Petition), 388–409 (Sept. 12, 2013 Citizen Petition), 410–69 (Dec. 5, 2013 Citizen Petition), 493–555 (July 2, 2014 Citizen Petition), 564–696 (Mar. 31, 2015 Citizen Petition). Among other arguments, Teva contended that, because of the variability in Copaxone, an ANDA application could not satisfy the statutory "sameness" requirement for a generic drug. *See, e.g.*, *id.* at 437. Indeed, in each of its eight Citizen Petitions, Teva represented to FDA that the sequences of the polymer chains in Copaxone are neither specific nor predefined. To the contrary, in Teva's words, "[t]he . . . manufacturing process [for Copaxone] creates a mixture of polypeptides with different primary structures, chain lengths and conformations. It has been estimated that this mixture likely contains more than 10^{12} different polypeptides and theoretically could contain more than 10^{29} possible primary polypeptide sequences." *Id.* at 479. Using Teva's math, "more than a trillion unique polypeptides," with distinct sequences, make up glatiramer acetate, a substance which "could contain more than a trillion times a trillion different polypeptides (i.e., 100,000,000,000,000,000,000,000,000,000 different polypeptides)." *Id.* at 479 (emphasis omitted); *see also, e.g.*, *id.* at 24, 35, 38, 78, 184.

In its fourth Citizen Petition, submitted on June 4, 2012, Teva argued that under the definition of "protein" set forth in the 2012 Guidance Document, "many of the polypeptides comprising Copaxone appear to qualify as 'proteins.'" *Id.* at 342–43; *see also id.* at 346 n.10. FDA's denial of that Petition explained, based on the 2011 Memorandum and the 2012 Guidance Document, that the agency "interprets the statutory term 'protein' to exclude amino acid polymers that lack a 'specific defined sequence'" and that "[a]s a result of its random polymerization process, Copaxone does not have a specific, defined sequence." *Id.* at 383 n.33.

On April 16, 2015, FDA denied Teva's last Citizen Petition and approved an ANDA for Sandoz's generic glatiramer acetate product in a forty-three page letter. *Id.* at 697, 699; *see also id.* at 697–739; Sandoz Mem. at 16. FDA explained that "[c]urrent analytical techniques are capable of supporting a demonstration of active ingredient sameness between the generic glatiramer acetate injection and [Copaxone]." AR at 727; *see also id.* at 727–31. The agency agreed with Teva's characterization of Copaxone's inherent variability and internal diversity, finding that "active ingredient sameness criteria for a generic glatiramer acetate injection should incorporate this batch-to-batch variability." *Id.* at 718 n.69. FDA developed four criteria to assess sameness for generic glatiramer acetate products: "(1) Fundamental reaction scheme; (2) Physiochemical properties including composition; (3) Structural signatures for polymerization and depolymerization; and (4) Results in a biological assay." *Id.* at 700. Just as it did in denying Teva's fourth Citizen Petition, FDA again observed that "glatiramer acetate is distinguishable from proteins because (unlike a protein) it does not . . . have a defined and specific amino acid sequence," and "there is a negligible likelihood of having identical amino acid sequences along entire copolymer chains from batch to batch." *Id.* at 708 (footnotes omitted). Additional ANDAs for Copaxone, including an ANDA for a generic product submitted by Mylan, were

approved in 2017 and 2018. Federal Defs.' Mem. Law Supp. Cross-Mot. Summ. J. & Opp'n Pls.' Mot. Summ. J. at 4 ("Fed. Defs.' Mem."), ECF No. 36-1.

3. BPCIA Transition Provision and Glatiramer Acetate Products

On March 14, 2016, FDA announced a new draft guidance document, open to public comment, for implementing the BPCIA's transition provision, BPCIA § 7002(e)(4), which applied the definitions of "protein" and "chemically synthesized polypeptide" set forth in its 2011 Memorandum and the 2012, 2015, and 2016 Guidance Documents. *See* AR at 780–95. FDA read § 7002(e)(4) to require that "on March 23, 2020, applications for biological products that have been approved under [the FDCA] will no longer exist as [NDAs or ANDAs] and will be replaced by approved [BLAs] under [the PHSA]." *Id.* at 790. The agency also provided a list of examples of biological products then approved under NDAs or ANDAs that would be transitioned to BLAs. *Id.* at 795. Glatiramer acetate products were not on this 2016 list of biological products to be transitioned to BLAs. *See id.*

On December 12, 2018, the same day that FDA issued its Proposed Rule codifying its interpretations of "protein" and "chemically synthesized polypeptides," FDA finalized this guidance, which was again open to public comment, *see id.* at 873–99, and posted a preliminary list of Transition Products, that is, biological products operating under approved NDAs that would be deemed to be BLAs on March 23, 2020 (the "Preliminary List"), *id.* at 900–09. Neither Copaxone nor any other glatiramer acetate product was included on the 2018 list, *see id.*, or on FDA's September 2019 and January 2020 updates to the Preliminary List, *see id.* at 1133–42, 1143–51.

On February 19, 2020, Teva submitted its first and only comments to the docket regarding the Preliminary List. *Id.* at 1008–23. Raising many of the same arguments as in this litigation, Teva contended that, because Congress had eliminated the parenthetical exception for

chemically synthesized polypeptides in the 2019 Act, Copaxone now qualified as a protein because, in addition to satisfying FDA's forty amino acid size requirement, it has a "specific, defined sequence." *Id.* at 1015. In support of this view, Teva argued that "while the overall sequence of each individual polymer within the glatiramer acetate mixture may differ both within a single batch and from batch-to-batch, the conservation of local amino acid sequences among the polymers reflects a sufficiently specific and defined sequence to qualify as a 'protein,'" *id.* at 1016, and compared Copaxone to two naturally derived products included on the Preliminary List, Vitrase (hyaluronidase) and Creon (pancrelipase), that, in Teva's view, have "undefined and unspecified overall amino acid sequences," *id.*, but were nonetheless classified as proteins, *id.* at 1016–18. In the alternative, Teva argued that, at a minimum, Copaxone is "analogous" to either a protein or a vaccine. *See id.* at 1019–22.

On March 20, 2020, three days before the BPCIA transition deadline of March 23, 2020, FDA issued an internal decision memorandum in which it determined that Copaxone is not a biological product and therefore would not be transitioned to a BLA (the "Decision Memorandum"). *Id.* at 1117–23. Applying the definition adopted in the Final Rule, the agency found that "[g]latiramer acetate is not a 'protein' because it does not have a specific, defined sequence," a criterion which "describes the manner in which specific amino acids are added to a polymer in a defined sequence." *Id.* at 1120. FDA explained that "[n]aturally occurring and recombinant proteins are made as the result of the synthesis of RNA [ribonucleic acid] from a DNA template (transcription) followed by translation into a protein molecule" and so "[f]or such proteins, the existence of a DNA template renders the sequence 'specific and defined.'" *Id.* Synthetic proteins, too, must have a specific, defined sequence, which typically is "generated by the stepwise addition of specific amino acids in a defined sequence" during synthesis. *Id.*

Copaxone, in contrast, exhibits "sequence variability" because "the sequences are driven by reaction chemistry rather than a pre-defined template." *Id.* Though patterns may recur due to the chemical properties of the amino acids that compose glatiramer acetate, exact replication of any single sequence is not assured. FDA next found that Copaxone is not "analogous" to either a protein or a vaccine, explaining that "it would not be appropriate 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' set forth in FDA's" Final Rule. *Id.* at 1121. Thus, FDA "would not consider an amino acid sequence that does not have a specific, defined sequence to be 'analogous' to a protein." *Id.*

On March 23, 2020, FDA transitioned ninety-six NDAs to BLAs, in accordance with § 7002(e)(4) of the BPCIA. *Id.* at 1124–32. The final list of transitioned products included several amino acid polymers with specific, defined sequences and lengths between forty and ninety-nine amino acids that initially had been excluded from the Preliminary List because they were chemically synthesized, but were deemed eligible for transition upon the 2019 Act's deletion of the parenthetical exclusion. All transitioned products were determined by FDA to be a protein or analogous to a protein. Fed. Defs.' Mem. at 12. Copaxone was not on the list and therefore was not transitioned to a BLA.

C. Procedural Background

The day after the BPCIA transition deadline, on March 24, 2020, Teva initiated this action, filing a two-count complaint alleging that FDA's denial of Teva's Transition Request violated section 706(2)(A) of the Administrative Procedure Act ("APA"), 5 U.S.C. § 706(2)(A), section 351 of the PHSA, 42 U.S.C. § 262(i)(1), and section 7002(e)(4) of the BPCIA and seeking declaratory and injunctive relief. Compl. ¶¶ 75–89. The parties proposed entry of an order expediting briefing on the merits in to order to avoid a motion for preliminary injunction.

Joint Mot. Entry of Scheduling Order, ECF No. 7. Consistent with the parties' request, the Court entered a scheduling order for expedited briefing on cross-motions for summary judgment. Min. Order (Apr. 9, 2020). On April 17, 2020 and April 24, 2020, respectively, Sandoz and Mylan filed motions to intervene, *see* Mot. Intervene by Sandoz Inc.; Mot. Intervene as Def., which motions were granted, *see* Min. Order (Apr. 20, 2020); Min. Order (Apr. 27, 2020).

Briefing proceeded under the parties' schedule, as modified, *see* Min. Order (June 22, 2020), with the final briefs filed on July 30, 2020, *see* Federal Defs.' Reply Mem. Supp. Cross-Mot. Summ. J. ("Fed. Defs.' Reply"), ECF No. 43; Sandoz Inc.'s Reply Mem. Supp. Mot. Summ. J. ("Sandoz Reply"), ECF No. 44; Mylan's Reply Mem. Supp. Mylan's Cross-Mot. Summ. J. ("Mylan Reply"), ECF No. 45. Upon the Court's order, *see* Min. Order (Dec. 10, 2020), the parties also submitted supplemental briefing, *see* Suppl. Br. Supp. Pls.' Mot. Summ. J. ("Pls.' Suppl. Br."), ECF No. 49; Sandoz Inc.'s Resp. Pls.' Suppl. Br. ("Sandoz Suppl. Br."), ECF No. 50; Mylan's Resp. Pls.' Suppl. Br. ("Mylan Suppl. Br."), ECF No. 51; Fed. Defs.' Resp. Pls.' Suppl. Br. on Cross-Mots. Summ. J. ("Fed. Defs.' Suppl. Br."), ECF No. 52, which was completed by December 17, 2020. The parties' cross-motions for summary judgment are now ripe for resolution.

II. LEGAL STANDARD

A. Administrative Procedure Act

The APA provides for judicial review of any "final agency action for which there is no other adequate remedy in a court," 5 U.S.C. § 704, and "instructs a reviewing court to set aside agency action found to be 'arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law,'" *Cigar Ass'n of Am. v. FDA*, 964 F.3d 56, 61 (D.C. Cir. 2020) (quoting 5 U.S.C. § 706(2)(A)). This standard "'requires agencies to engage in reasoned decisionmaking,' and . . . to reasonably explain to reviewing courts the bases for the actions they take and the

conclusions they reach." *Brotherhood of Locomotive Eng'rs & Trainmen v. Fed. R.R. Admin.*, 972 F.3d 83, 115 (D.C. Cir. 2020) (quoting *Dep't of Homeland Sec. v. Regents of Univ. of Cal.* ("*Regents*"), 140 S. Ct. 1891, 1905 (2020)). Judicial review of agency action is limited to "'the grounds that the agency invoked when it took the action,'" *Regents*, 140 S. Ct. at 1907 (quoting *Michigan v. EPA*, 576 U.S. 743, 758 (2015)), and the agency, too, "must defend its actions based on the reasons it gave when it acted," *id.* at 1909.

B. Summary Judgment

Pursuant to Federal Rule of Civil Procedure 56, "'[a] party is entitled to summary judgment only if there is no genuine issue of material fact and judgment in the movant's favor is proper as a matter of law.'" *Soundboard Ass'n v. FTC*, 888 F.3d 1261, 1267 (D.C. Cir. 2018) (quoting *Ctr. for Auto Safety v. Nat'l Highway Traffic Safety Admin.*, 452 F.3d 798, 805 (D.C. Cir. 2006)); *see also* Fed. R. Civ. P. 56(a). In APA cases such as this one, involving cross-motions for summary judgment, "the district judge sits as an appellate tribunal. The 'entire case' on review is a question of law." *Am. Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1083 (D.C. Cir. 2001) (footnote omitted) (collecting cases). Thus, this Court need not and ought not engage in lengthy fact finding, since "[g]enerally speaking, district courts reviewing agency action under the APA's arbitrary and capricious standard do not resolve factual issues, but operate instead as appellate courts resolving legal questions." *James Madison Ltd. by Hecht v. Ludwig*, 82 F.3d 1085, 1096 (D.C. Cir. 1996); *see also Lacson v. U.S. Dep't of Homeland Sec.*, 726 F.3d 170, 171 (D.C. Cir. 2013) (noting, in an APA case, that "determining the facts is generally the agency's responsibility, not ours"). As a general rule, judicial review is limited to the administrative record, since "[i]t is black-letter administrative law that in an [APA] case, a reviewing court should have before it neither more nor less information than did the agency when it made its

decision." *CTS Corp. v. EPA*, 759 F.3d 52, 64 (D.C. Cir. 2014) (second alteration in original) (internal quotation omitted).

III. DISCUSSION

Teva challenges the Decision Memorandum on several grounds. First, it contends that FDA's Final Rule interpreting the term "protein" is invalid because the Rule is procedurally deficient and the interpretation is contrary to section 351 of the PHSA. Thus, Teva argues, both the Final Rule and the Decision Memorandum applying it are invalid. Next, Teva submits that, even if FDA's interpretation of "protein" is valid on its face, FDA's application of that definition in the Decision Memorandum to refuse to treat Copaxone as a protein, as well as its determination that Copaxone is not a product "analogous" to a protein, was arbitrary and capricious. Defendants disagree with each contention and argue that Teva does not have standing to bring any of its challenges. Teva's standing to bring this action is considered first before turning to the parties' arguments on the merits.

A. Teva Has Standing

Article III requires that plaintiffs establish "the irreducible constitutional minimum of standing," *Lujan v. Defs. of Wildlife*, 504 U.S. 555, 560 (1992), that they have "(1) suffered an injury in fact, (2) that is fairly traceable to the challenged conduct of the defendant, and (3) that is likely to be redressed by a favorable judicial decision," *Spokeo, Inc. v. Robins*, 136 S. Ct. 1540, 1547 (2016) (citing *Lujan*, 504 U.S. at 560–61; *Friends of the Earth, Inc. v. Laidlaw Env't Servs. (TOC), Inc.*, 528 U.S. 167, 180–81 (2000)); *see also Louie v. Dickson*, 964 F.3d 50, 54 (D.C. Cir. 2020). "The absence of any one of these three elements defeats standing." *Newdow v. Roberts*, 603 F.3d 1002, 1010 (D.C. Cir. 2010). Plaintiffs carry the burden of establishing the elements of standing "'with the manner and degree of evidence required at the successive stages of the litigation.'" *Bennett v. Spear*, 520 U.S. 154, 168 (1997) (quoting *Lujan*, 504 U.S. at 561).

At summary judgment, "the plaintiff 'must set forth by affidavit or other evidence specific facts' that prove standing." *Humane Soc'y of U.S. v. Perdue*, 935 F.3d 598, 602 (D.C. Cir. 2019) (quoting *Lujan*, 504 U.S. at 561) (citing *Scenic Am., Inc. v. U.S. Dep't of Transp.*, 836 F.3d 42, 49 n.3 (D.C. Cir. 2016)).

The parties' standing dispute centers on the first element requiring that Teva have suffered an injury-in-fact "that is 'concrete and particularized' and 'actual or imminent, not conjectural or hypothetical.'" *Spokeo, Inc.*, 136 S. Ct. at 1548 (quoting *Lujan*, 504 U.S. at 560). Teva defends its standing on three grounds, any one of which, in its view, demonstrates constitutional standing under Article III and statutory standing. Specifically, Teva alleges three injuries resulting from FDA's refusal to transition Copaxone from an NDA to a BLA: (1) "an informational injury"; (2) "the loss of statutory rights," namely, "the ability to receive confidential access to a biosimilar applicant's aBLA and to file an infringement lawsuit"; and (3) "a competitive injury." Pls.' Mem. P. & A. Supp. Mot. Summ. J. ("Pls.' Mem.") at 17, ECF No. 31-1; *see also* Pls.' Consolidated Opp'n Defs.' & Intervenor-Defs.' Cross-Mots. Summ. J. & Reply Supp. Pls.' Mot. Summ. J. ("Pls.' Opp'n") at 4–15, ECF No. 40. Defendants dispute that Teva has constitutional standing based on any of these three injuries, which, they contend, are too speculative to constitute injuries-in-fact. As explained below, Teva's competitive injury confers both constitutional and statutory standing.

1. Teva Has Shown Sufficient Injury-in-Fact for Standing

The sufficiency for standing of each of Teva's alleged injuries in fact is examined in turn. Teva claims to suffer both an "informational injury" and the deprivation of its statutory process right to bring a preapproval patent infringement lawsuit due to the continued regulation of Copaxone and generic glatiramer acetate products under the FDCA. As to the alleged "informational injury," Teva explains that manufacturers of competing glatiramer acetate

products have no obligation to provide Teva with information about their ANDA applications and the manner in which they manufacture their products under the FDCA, but these competitors would have such an obligation to supply, and Teva would have a concomitant right to receive, that information if Copaxone were classified as a biological product under the PHSA. Pls.' Mem. at 17–18; Pls.' Opp'n at 5–11.

Relatedly, Teva contends that FDA's failure to transition Copaxone to a BLA deprives Teva of statutory process rights, under the BPCIA's amendments to the PHSA, to which it would be entitled as a holder of a BLA. Pls.' Mem. at 17–18; Pls.' Opp'n at 5–11. If Copaxone were regulated as a biologic under the BPCIA's amendments to the PHSA, manufacturers of prospective biosimilars would be required to provide Teva with a copy of their aBLA applications, "information that describes the process or processes used to manufacture the [biosimilars]," 42 U.S.C. § 262(l)(2)(A), and 180 days' notice before commercially marketing the biosimilar, *id.* § 262(l)(8)(A); *see supra* Part I.A.2. Teva claims that this information, in combination with the BPCIA's detailed provision for the preapproval resolution of patent disputes, *see supra* Part I.A.2, would enable enforcement of the patents Teva holds for the process of manufacturing glatiramer acetate against a prospective biosimilar applicant, facilitate the "patent dance," and allow Teva to bring an infringement suit or a declaratory judgment action prior to approval of the biosimilar. Pls.' Mem. at 17–18; Pls.' Opp'n at 5–11. In contrast, the FDCA does not require ANDA applicants seeking to manufacture generic drugs to provide any information about their manufacturing processes (or any other information not covered by an Orange Book patent) in their Paragraph IV certifications and does not provide for preapproval infringement challenges based on process patents or other patents not included in the Orange Book. *See* 21 U.S.C. § 355(b)(1), (j)(2)(B)(iv); *supra* Part I.A.1; Pls.' Opp'n at 6. Thus, as long

as Copaxone continues to be treated as a drug, Teva has no recourse to enforce its patents against a prospective ANDA applicant.

Teva contends that these alleged injuries are "actual and imminent" because "a generic drug manufacturer, through litigation counsel, has informed Teva that it intends to file an ANDA to market a generic version of COPAXONE." Pls.' Opp'n at 7; *see also* Pls.' Mem. at 17; Ragan Decl. ¶ 8. To date, however, no such ANDA has been filed. As a rule, "litigants cannot establish an Article III injury based on the 'independent action[s] of some third party not before th[is] court' . . . because 'predictions of future events (especially future actions taken by third parties)' are too speculative to support a claim of standing." *Turlock Irrigation Dist. v. FERC*, 786 F.3d 18, 25 (D.C. Cir. 2015) (alterations in original) (first quoting *Fla. Audubon Soc'y v. Bentsen*, 94 F.3d 658, 670 (D.C. Cir. 1996) (en banc); and then quoting *United Transp. Union v. Interstate Commerce Comm'n*, 891 F.2d 908, 912 (D.C. Cir. 1989)). For Teva's alleged injuries to occur, a generic manufacturer would have to submit an ANDA that was then accepted for review and approved by FDA. *See* Fed. Defs.' Reply at 4–6. This chain of events, which relies on the actions of an unidentified third party as its catalyst, is, at first blush, too speculative to support standing.

Defendants further argue that, even if a prospective generic manufacturer came forward, Teva would not actually enjoy the rights it asserts to either information or statutory process under the PHSA for two reasons. As defendants explain, the BPCIA's information-sharing provision is enforceable only through the declaratory-judgment action provided in 42 U.S.C. § 262(l)(9)(C), *see Sandoz*, 137 S. Ct. at 1675, and therefore does not create an unambiguous right for sponsors to receive information from biosimilar applicants. Fed. Defs.' Mem. at 14–16; Mylan Mem. at 21–23; Sandoz Mem. at 22–24; Fed. Defs.' Reply at 4–6; Mylan Reply at 8–10;

Sandoz Reply at 4–10. In addition, neither section 351 of the PHSA nor 35 U.S.C. § 271(e)(2)(C)(ii) allow patent holders to bring preapproval patent infringement suits to enforce process patents. Fed. Defs.' Mem. at 14–17; Mylan Mem. at 21–23; Sandoz Mem. at 22–23; Mylan Reply at 8–10; Sandoz Reply at 5–10. Neither of these questions of statutory interpretation need be resolved here, however, because Teva's alleged competitive injury is sufficient to confer Article III standing.

(a) Alleged Competitive Injury

Teva alleges a "competitive," or economic, injury, because, under the automatic substitution laws applicable to prescriptions for "drugs," prescriptions written for Copaxone are automatically filled with a generic glatiramer acetate product manufactured by one of Teva's competitors. Indeed, when FDA has approved both an NDA for a brand-name drug and an ANDA for a generic drug, the relevant laws of every state allow (and in some cases require) pharmacists filling a prescription for the brand-name drug automatically to dispense the generic drug in its place, unless the prescribing physician specifically directs the pharmacist to "dispense as written." Pls.' Mem. at 18–19; *see, e.g.*, D.C. Code §§ 48-803.02, .03(2); *see also* Pls.' Opp'n at 11–12; Decl. of Dalton Tomlinson ("Tomlinson Decl.") ¶¶ 7–8, ECF No. 40-2. Thus, a pharmacist filling a prescription written for Copaxone is likely to dispense a generic glatiramer acetate product (for example, those manufactured by Mylan or Sandoz) rather than Teva's brand-name product.

These automatic substitution laws do not apply to biologics and, consequently, Teva contends that, if Copaxone had been transitioned to a BLA, prescriptions written for Copaxone would be filled with Teva's product, at least until FDA approved a biosimilar as "interchangeable" with Copaxone. Pls.' Mem. at 18–19. In some states, substitution is not

available at all if a biological product is prescribed by name. *See, e.g.*, D.C. Code §§ 48-803.02(a)(1), .03(2)(A); Tomlinson Decl. ¶ 14. If Copaxone were treated as a biological product, in these jurisdictions, a pharmacist filling a prescription written for Copaxone would have to dispense Teva's product rather than a biosimilar produced by Mylan, Sandoz, or any other manufacturer. The majority of jurisdictions allow biosimilars to be substituted for biological products, but only after a finding by FDA that the biosimilar is "interchangeable" with the biological product. *See, e.g.*, Fla. Stat. § 465.0252(1), (2); Va. Code §§ 54.1-3401, 54.1-3408.04(A). Interchangeability is a heightened requirement separate from aBLA approval, with no equivalent in the generic drug context. *See* 42 U.S.C. § 262(i)(3), (k)(4); AR at 960–72. Thus, even in jurisdictions that allow substitution of biological products, if Copaxone were a biological product, unless and until FDA determined that a biosimilar was interchangeable with Copaxone, prescriptions written for Copaxone would be filled with Teva's product. *See* Pls.' Mem. at 18–19; Pls.' Opp'n at 11–15.

"When determining whether a plaintiff has Article III standing, the court must assume that the [plaintiff] will prevail on the merits." *Comm. on Judiciary of U.S. House of Representatives v. McGahn*, 968 F.3d 755, 762 (D.C. Cir. 2020) (en banc) (citations omitted); *see also Estate of Boyland v. U.S. Dep't of Agric.*, 913 F.3d 117, 123 (D.C. Cir. 2019). Assuming, then, that Teva will prevail on its claim that Copaxone should have been transitioned to a BLA on March 23, 2020, Teva is injured every time a pharmacist dispenses a generic glatiramer acetate product in place of Copaxone because each sale of a generic drug while Copaxone continues to be regulated under the FDCA would likely translate to a sale of Copaxone if Copaxone were regulated under the PHSA. In the regulatory landscape described above, currently, patients who fill prescriptions for Copaxone receive generic glatiramer acetate

products unless their provider writes "dispense as written" or "do not substitute" on the prescription. Tomlinson Decl. ¶ 7.

Teva's Vice President for Specialty Product Marketing has stated that in April and May 2020, the two months immediately following the BPCIA's deadline to transition qualifying products to BLAs and aBLAs, at least 3,925 prescriptions were written for Copaxone without specifying that the prescription should be dispensed as written. *Id.* ¶ 8.[3] If all glatiramer acetate products had been transitioned to BLAs and aBLAs on March 23, 2020, pharmacists would have dispensed, and would continue to dispense, Copaxone in filling these thousands of prescriptions until FDA determines that another glatiramer acetate product is interchangeable with Copaxone. As Copaxone continues to be regulated as a drug, these prescriptions were likely filled with a generic product, depriving Teva of sales it would have enjoyed if Copaxone had been transitioned on March 23, 2020. Thus, taking as true Teva's claim that Copaxone should have been transitioned to a BLA, Teva has accumulated and continues to accumulate monetary losses, in the form of lost sales, from the improper automatic substitution of generic glatiramer acetate

[3] The federal defendants assert that this statistic, provided in a declaration by Vice President for Specialty Product Marketing, is inadmissible under Federal Rule of Civil Procedure 56(c)(4), which requires that declarations in support of motions for summary judgment "must be made on personal knowledge, set out facts that would be admissible in evidence, and show that the affiant or declarant is competent to testify on the matters stated," Fed. R. Civ. P. 56(c)(4), because the declarant does not identify its source. Fed. Defs.' Reply at 7. Rule 56(c)(4)'s "'directive with respect to the admissibility of an affidavit's [or a declaration's] contents on summary judgment has been liberally construed,'" *Sabra ex rel. Baby M v. Pompeo*, 453 F. Supp. 3d 291, 330 (D.D.C. 2020) (quoting *Londrigan v. FBI*, 670 F.2d 1164, 1174 (D.C. Cir. 1981)), but its "requirement of personal knowledge . . . is unequivocal, and cannot be circumvented," *Londrigan*, 670 F.2d at 1174 (footnote omitted). The declarant here attests that his declaration "is based upon [his] personal knowledge, including [his] experience in the pharmaceutical industry and at Teva," Tomlinson Decl. ¶ 1, states that he is "responsible for the planning and management of CNS, Psychiatry, and Pain Care products in the United States," *id.* ¶ 3, and "declare[s] under penalty of perjury" that his declaration is "true and correct," *id.* at 5. Given the declarant's position in Teva's marketing department and representations in his sworn statement, the requisite "personal knowledge" of the rate of prescription for Copaxone and related products may be inferred. *Cf. Wye Oak Tech., Inc. v. Republic of Iraq*, No. 1:10-cv-01182-RCL, 2018 WL 5983385, at *7–8 (D.D.C. Nov. 14, 2018) (finding a declarant's statements that they were "authorized and qualified to make the declaration based on [their] position[s]" and certification that their declarations were "'true and correct' under the penalty of perjury" sufficient to "satisfy the low bar set forth in Rule 56's personal knowledge requirement").

products for Copaxone since March 23, 2020. Such "[e]conomic harm . . . clearly constitutes an injury-in-fact." *Carpenters Indus. Council v. Zinke*, 854 F.3d 1, 5 (D.C. Cir. 2017).[4]

Defendants challenge Teva's competitive injury on two main grounds. First, they contend that "[i]t is pure speculation that if the Teva, Mylan, and Sandoz glatiramer acetate products were transitioned to BLAs, physicians would change their prescribing habits by writing their prescriptions in a way that would require their patients to use the Teva product." Fed. Defs.' Reply at 8; *see also, e.g., id.* at 6–8; Fed. Defs.' Mem. at 16–18; Sandoz Reply at 10–11. Given that thousands of Copaxone prescriptions are currently written without "dispense as written" instructions, *see* Tomlinson Decl. ¶ 8, third-party behavior need not change at all for Teva to demonstrate actual and imminent harm. The continuation of the status quo with respect to third-party behavior, accompanied by classification of Copaxone as a biologic, would ensure an increase in Teva's sales. Defendants' theory, that prescribers who currently write prescriptions for Copaxone would begin to write prescriptions specifically for glatiramer acetate products made by Mylan or Sandoz were the products transitioned to BLAs and aBLAs, relies more on a speculative change in prescriber behavior than does Teva's.

The federal defendants next argue that "Teva's prediction that FDA would not find [biosimilars] to be interchangeable with Copaxone is speculative." Fed. Defs.' Mem. at 17. This arguments fails for two reasons. First, in jurisdictions that do not allow substitution of biologics,

[4] Defendants argue that because "Teva did not raise this allegation in its complaint," Teva may not rely on this theory of standing. Fed. Defs.' Mem. at 17; *see also* Mylan Reply at 10 & n.7. In its Complaint, Teva alleged injury-in-fact resulting from the treatment of competitor glatiramer acetate products as generic drugs rather than biosimilars, Compl. ¶¶ 68–70, and described the interchangeability requirement for the substitution of biosimilars, *id.* ¶ 35. At the pleading stage, "'general factual allegations of injury resulting from the defendant's conduct may suffice'" to demonstrate standing, *Osborn v. Visa Inc.*, 797 F.3d 1057, 1063 (D.C. Cir. 2015) (quoting *Lujan*, 504 U.S. at 561), and courts "'grant[] plaintiff[s] the benefit of all inferences that can be derived from the facts alleged,'" *Am. Nat'l Ins. Co. v. FDIC*, 642 F.3d 1137, 1139 (D.C. Cir. 2011) (quoting *Thomas v. Principi*, 394 F.3d 970, 972 (D.C. Cir. 2005)). The allegations in Teva's Complaint were thus sufficient to support Teva's claim of competitive injury at that stage.

prescriptions for Copaxone would continue to be filled with Teva's product even after a finding of interchangeability and thus Teva's losses from prescriptions in these states are "actual and imminent" regardless of FDA's eventual interchangeability determinations. Second, even if FDA found a biosimilar to be interchangeable with Copaxone, had Copaxone been transitioned on March 23, 2020, Teva's product would still have been dispensed to fill prescriptions for Copaxone in jurisdictions that allow substitution from that date until the effective date of the interchangeability decision. These interim losses are not speculative and are sufficient for standing purposes.

(b) Causation and Redressability

The remaining two elements of standing—causation and redressability—"'overlap as two sides of a causation coin.'" *Exhaustless Inc. v. FAA*, 931 F.3d 1209, 1212 (D.C. Cir. 2019) (quoting *Dynatlantic Corp. v. Dep't of Def.*, 115 F.3d 1012, 1017 (D.C. Cir. 1997)). "When a petitioner itself is the object of the challenged agency action," as Teva is here, "there usually is little doubt of causation." *Id.* (citing *Lujan*, 504 U.S. at 561–62). Indeed, none of the parties dispute causation, but Mylan (though not the federal defendants or Sandoz) contends that Teva's requested relief, an injunction directing FDA to reclassify Copaxone as a biological product, is not likely to redress its alleged competitive injury because, for Teva's competition from generic glatiramer acetate products to decrease, FDA would have to reclassify the underlying ANDAs as aBLAs and then determine that the biosimilars are not interchangeable with Copaxone. The number of steps required, in Mylan's view, makes the redressability of Teva's alleged harm by an injunction speculative at best. Mylan Mem. at 23–24; Mylan Reply at 10–11.

The chain of events Mylan outlines overlooks the obvious: an injunction reclassifying Copaxone as a biologic would immediately exempt prescriptions written for Copaxone from

automatic substitution laws. That fact alone would redress at least some of Teva's harms, regardless of whether or when FDA transitioned the ANDAs to aBLAs or made an interchangeability finding. The degree to which the reclassification of Copaxone would relieve Teva's injuries may be limited by an eventual finding of interchangeability, as Mylan suggests, but the clear ability of the requested injunction to redress a wide swath of Teva's economic harms in the interim is not speculative simply because it may be short-lived.[5] Further, the mere possibility "that a hypothesized future event"—in this case, a prospective interchangeability determination—"might injure [a plaintiff] in the same way as the challenged agency decision" does not leave a plaintiff without standing. *Braeburn Inc. v. FDA*, 389 F. Supp. 3d 1, 16 (D.D.C. 2019). Teva need not disprove any speculative harm it may experience as the result of a future interchangeability finding in order to access judicial relief. *See Duke Power Co. v. Carolina Env'tl Study Grp., Inc.*, 438 U.S. 59, 78 (1978) ("Nothing in our prior cases requires a party seeking to invoke federal jurisdiction to negate the kind of speculative and hypothetical possibilities suggested in order to demonstrate the likely effectiveness of judicial relief."); *Int'l Ladies' Garment Workers' Union v. Donovan*, 722 F.2d 795, 811 (D.C. Cir. 1983) ("The appellants need not negate every conceivable impediment to effective relief no matter how speculative, nor are they required to *prove* that granting the requested relief is certain to alleviate their injury." (internal citation and quotation omitted)). Even after an interchangeability

[5] In addition, the intervenor-defendants appear to have conceded that, even if FDA ultimately found their products to be interchangeable with Copaxone, their sales would suffer, and Teva's would benefit, while FDA considered the interchangeability question. *See* Sandoz Inc.'s Mem. Supp. Unopposed Mot. Intervene at 7–8, ECF No. 9-1 ("[T]o the extent FDA were to transition Sandoz's ANDAs to BLAs, yet delay in making an interchangeability determination . . . Sandoz would lose its ability to compete effectively in the market with Copaxone."); Mylan's Mem. P. & A. Supp. Mylan's Unopposed Mot. Intervene at 8, ECF No. 19-1 ("If the court were to adopt Teva's . . . position, Mylan would have to incur substantial costs in resolving uncertainty regarding its [glatiramer acetate] products.").

determination, an injunction would continue to remedy Teva's competitive injury in those jurisdictions that do not allow substitution of biosimilars.

In sum, FDA's failure to transition Copaxone to a BLA on March 23, 2020 has deprived and continues to deprive Teva of sales of Copaxone. This competitive and economic harm is an actual and imminent, concrete and particularized injury, fairly traceable to FDA's determination, and redressable by a favorable judicial decision. Teva has constitutional standing.

2. Teva Has Statutory Standing

Next, Sandoz, but not the federal defendants or Mylan, challenges Teva's statutory standing under the BPCIA. *See* Sandoz Mem. at 23–26; Sandoz Reply at 10–12. Statutory standing is not, as Sandoz contends, a question of "prudential standing," Sandoz Mem. at 24, but instead "a straightforward question of statutory interpretation," *Lexmark Int'l, Inc. v. Static Control Components, Inc.*, 572 U.S. 118, 129 (2014), that determines "who may invoke the cause of action in" a particular statute through the "zone-of-interests" test, *id.* at 130. In the APA context, "the zone-of-interests test is not 'especially demanding,'" *Indian River Cnty., Fla. v. U.S. Dep't of Transp.*, 945 F.3d 515, 529 (D.C. Cir. 2019) (quoting *Match-E-Be-Nash-She-Wish Band of Pottawatomi Indians v. Patchak*, 567 U.S. 209, 225 (2012)), and "'forecloses suit only when a plaintiff's interests are so marginally related to or inconsistent with the purposes implicit in the [substantive] statute that it cannot reasonably be assumed that Congress intended to permit the suit,'" *id.* at 530 (quoting *Patchak*, 567 U.S. at 225); *see also Mendoza v. Perez*, 754 F.3d 1002, 1016–17 (D.C. Cir. 2014).

Sandoz contends that Teva falls outside the zone of interests protected by the BPCIA because, first, "standing does not automatically arise from being regulated by the statute-at-issue, nor can it arise from a mere failure to impose stricter regulations on competitors," Sandoz Mem. at 25, and, second, "*increasing* competition is within the zone of interests of the BPCIA, but

suppressing competition as Teva seeks to do here, is not," Sandoz Reply at 11; *see also* Sandoz Mem. at 24–25. Neither argument is persuasive. The BPCIA expressly requires FDA to transition NDAs for products that would have been classified as biologics in the first instance under the revised definition to BLAs. *See* BPCIA § 7002(e)(4). Teva holds an NDA for Copaxone that allegedly should have been transitioned to a BLA under that provision and therefore has an interest in its product being regulated by FDA under the appropriate statute. That interest is clearly and directly related to the BPCIA's purpose of regulating all complex therapeutic products that qualify as biologics under the PHSA rather than the FDCA. The zone-of-interests test requires nothing more.

B. FDA's Interpretation of "Protein" Is Reasonable

Turning to the merits, Teva first contends that FDA's interpretation of the term "protein" in section 351's definition of "biological product," which was applied to Copaxone in the Decision Memorandum, is contrary to the statute, such that the interpretation, and the Decision Memorandum that relies on it, are "not in accordance with law." 5 U.S.C. § 706(2)(A); *see* Pls.' Mem. at 20–27; Pls.' Opp'n at 18–26. An agency's interpretation of a statute it administers is reviewed under the familiar two-step inquiry set forth in *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.* ("*Chevron*"), 467 U.S. 837 (1984); *see, e.g.*, *Cal. Cmtys. Against Toxics v. EPA*, 928 F.3d 1041, 1053 (D.C. Cir. 2019), so long as "Congress delegated authority to the agency generally to make rules carrying the force of law" and "the agency's interpretation claiming deference was promulgated in the exercise of that authority," *United States v. Mead Corp.*, 533 U.S. 218, 226–27 (2001); *see also Guedes v. Bureau of Alcohol, Tobacco, Firearms & Explosives*, 920 F.3d 1, 20 (D.C. Cir. 2019), *cert. denied*, 140 S. Ct. 789 (2020) (mem.). Under this standard, "[o]rdinarily, legislative rules receive *Chevron* deference," *Guedes*, 920 F.3d at 20, "[b]ut *Chevron* deference is not warranted where the regulation is

'procedurally defective'—that is, where the agency errs by failing to follow the correct procedures in issuing the regulation," *Encino Motorcars, LLC v. Navarro* ("*Encino I*"), 136 S. Ct. 2117, 2125 (2016) (quoting *Mead Corp.*, 533 U.S. at 227). Teva contends that the Final Rule, though a legislative rule, does not merit deference because it was improperly promulgated, *see* Pls.' Mem. at 20–22; Pls.' Opp'n at 18–21; Pls.' Suppl. Br. at 2–10, and that even if the Final Rule is procedurally sound, FDA's interpretation of "protein" fails under *Chevron*, *see* Pls.' Mem. at 22–27; Pls.' Opp'n at 21–26.[6] Each contention is taken in turn.

1. The Final Rule Is Reviewed Under Chevron

As a preliminary matter, Teva contends that FDA's interpretation of the term "protein," set forth in the Final Rule and applied to Copaxone in the Decision Memorandum, is not entitled to review under *Chevron*'s deferential standard because the Final Rule in which the definition was formally adopted is procedurally invalid. Teva argues that, because FDA "gave no opportunity to comment on Congress's decision to change the term being construed, by removing the parenthetical exclusion for 'chemically synthesized polypeptides' from 'protein'" after the passage of the 2019 Act, Teva and other interested parties were deprived of both fair notice and the ability to submit comments on FDA's proposed interpretation of the term "protein" in section 351 as amended by the 2019 Act. Pls.' Suppl. Br. at 6; *see also* Pls.' Mem. at 20–22; Pls.' Opp'n at 18–21. This procedural argument, which misconstrues both the effect of the 2019 Act and the terms FDA interpreted in the Final Rule and throughout the almost decade-long rulemaking process that preceded it, fails.

[6] Although Teva originally appeared to argue that the Final Rule was an interpretive rule, *see* Pls.' Mem. at 20, it concedes in its supplemental brief that the Final Rule is a legislative rule, albeit, in Teva's view, a procedurally deficient legislative rule, *see* Pls.' Suppl. Br. at 4–5.

In most cases, the APA requires a federal agency engaged in legislative rulemaking to follow notice-and-comment procedures. *See* 5 U.S.C. § 553(b). This process imposes on agencies the obligation "to provide the public with a notice of proposed rulemaking, an opportunity to comment, and, '[a]fter consideration of the relevant matter presented,' a 'concise general statement' of the rule's basis and purpose." *Sherley v. Sebelius*, 689 F.3d 776, 784 (D.C. Cir. 2012) (alteration in original) (quoting 5 U.S.C. § 553); *see also Perez v. Mortg. Bankers Ass'n*, 575 U.S. 92, 96 (2015) (describing the APA's "three-step procedure for . . . 'notice-and-comment rulemaking,'" during which "the agency must 'give interested persons an opportunity to participate in the rule making through submission of written data, views, or arguments'") (quoting 5 U.S.C. § 553(c)); *Cigar Ass'n of Am.*, 964 F.3d at 63–64 (same). A robust notice-and-comment process serves the "central purpose[s]" of "subject[ing] agency decisionmaking to public input . . .[,] obligat[ing] the agency to consider and respond to the material comments and concerns that are voiced," and "ensur[ing] the parties develop a record for judicial review." *Make the Road N.Y. v. Wolf*, 962 F.3d 612, 634 (D.C. Cir. 2020) (internal quotations and citations omitted); *see also Nat'l Ass'n of Clean Water Agencies v. EPA*, 734 F.3d 1115, 1148 (D.C. Cir. 2013) ("A purpose of notice-and-comment provisions under the APA . . . is 'to ensure that affected parties have an opportunity to participate in and influence agency decision making at an early stage, when the agency is likely to give real consideration to alternative ideas.'") (quoting *N.J., Dep't of Env'tl Prot. v. EPA*, 626 F.2d 1038, 1049 (D.C. Cir. 1980)).

As part of notice-and-comment rulemaking, the notice of proposed rulemaking must include "either the terms or substance of the proposed rule or a description of the subject and issues involved," 5 U.S.C. § 553(b), a requirement that has been construed to "to mean that the final rule the agency adopts must be a logical outgrowth of the rule proposed," *Long Island Care*

at Home, Ltd. v. Coke ("*Long Island Care*"), 551 U.S. 158, 174 (2007) (internal quotation omitted). "'A final rule is the logical outgrowth of a proposed rule if interested parties should have anticipated that the change was possible, and thus reasonably should have filed their comments on the subject during the notice-and-comment period.'" *Chesapeake Climate Action Network v. EPA*, 952 F.3d 310, 319 (D.C. Cir. 2020) (quoting *Clean Air Council v. Pruitt*, 862 F.3d 1, 10 (D.C. Cir. 2017) (per curiam)); *see also Idaho Conservation League v. Wheeler*, 930 F.3d 494, 508 (D.C. Cir. 2019) (same). A rule fails the logical outgrowth test if "'interested parties would have had to divine the agency's unspoken thoughts, because the final rule was surprisingly distant from the proposed rule.'" *Chesapeake Climate Action Network*, 952 F.3d at 319–20 (quoting *Clean Air Council*, 862 F.3d at 10). In other words, the public must have one clear chance to offer feedback on agency proposals, a requirement that is met "'if a new round of notice and comment would not provide commentators with their first occasion to offer new and different criticisms which the agency might find convincing.'" *Int'l Union, United Mine Workers of Am. v. Mine Safety & Health Admin.*, 626 F.3d 84, 95 (D.C. Cir. 2010) (quoting *Fertilizer Inst. v. EPA*, 935 F.2d 1303, 1311 (D.C. Cir. 1991)). "The object, in short, is one of fair notice," *Long Island Care*, 551 U.S. at 174; notice-and-comment processes that result in an unfair surprise being sprung on regulated entities are therefore deficient.

Set against this standard, FDA provided sufficient notice and multiple opportunities to comment on its interpretation of the statutory term "protein," even in light of the 2019 Act. The adequacy of the notice-and-comment procedures that culminated in FDA's promulgation of the Final Rule turns on whether Teva and other regulated entities had fair notice of, and at least one opportunity to respond to, the definition of "protein" set forth in the Final Rule.

Teva contends that the Final Rule is fatally flawed because "the Proposed Rule and the Final Rule were interpreting two materially different statutes" and FDA's original notice-and-comment process became null and void after the 2019 Act was passed. Pls.' Suppl. Br. at 6. Thus, Teva argues, FDA was required to undertake a new notice-and-comment process to provide an opportunity for comment on the impact of Congress's deletion of the parenthetical exception on FDA's interpretation of "protein" in the absence of the carve-out for "chemically synthesized polypeptides." Pls.' Mem. at 21–22; Pls.' Suppl. Br. at 5–10. This claim rests primarily on a mischaracterization of the term FDA purported to interpret in its Proposed Rule. FDA did not, as Teva asserts, "plan[] to adopt an interpretation of 'protein (except any chemically synthesized polypeptide),'" Pls.' Suppl. Br. at 1; *see also id.* at 6, which interpretation, after the enactment of the 2019 Act, the agency simply transferred unthinkingly, and without sufficient process, to the new statutory term "protein." Nor did FDA "rel[y] in part on a structural inference contrasting 'protein' with 'polypeptide' in the parenthetical exclusion," *id.* at 6, to develop its interpretation of protein.

Rather, from 2010 until the promulgation of the Final Rule in 2020, FDA consistently made plain that it was interpreting "protein" and "chemically synthesized polypeptide" independent of each other, as two distinct statutory terms. *See, e.g.*, AR at 121, 292, 328, 758, 787 n.3, 801–03. Indeed, the Proposed Rule indicated FDA's intent to codify the two definitions in separate sections of the Code of Federal Regulations. *See id.* at 807 (proposing to codify FDA's definition of "protein" at 21 C.F.R. § 600.3(h)(6) and FDA's definition of "chemically synthesized polypeptide" at 21 C.F.R. § 600.3(h)(7)). Further, though the structure of section 351's parenthetical exclusion informed FDA's decision to narrowly construe the term "chemically synthesized polypeptide" as meant to exclude a subset of otherwise-qualifying

"proteins" from biologic status, *see id.* at 305–06, 804, that consideration did not shape FDA's definition of "protein," as the more encompassing of the two terms, *see supra* Part I.A.4. FDA consistently understood the term "protein" to include chemically synthesized proteins, and the term "chemically synthesized polypeptides" to refer to a smaller group of chemically synthesized molecules that, although they met the agency's definition of "protein," would not be regulated as biologics because of the parenthetical exclusion. *See, e.g.*, AR at 803–05.

Given this minimal relationship between the terms "protein" and "chemically synthesized polypeptide" in FDA's interpretive framework, the 2019 Act's deletion of the parenthetical exception did nothing to change the meaning of the term "protein" standing alone. Its only effect was to eliminate the need for a regulatory definition of "chemically synthesized polypeptides" that, though they met the definitional criteria for "proteins," would not be treated as such because of the exception. FDA responded appropriately to this change in its Final Rule, which preserved and finalized the interpretation of "protein" FDA had first publicized in the 2011 Memorandum and 2012 Guidance Document, and, in light of the 2019 Act, removed FDA's separate interpretation of "chemically synthesized polypeptide." *See* AR at 1025–27.[7]

This background makes clear that FDA was not required to provide a new comment period after the enactment of the 2019 Act. The deletion of the parenthetical exclusion did not alter the term "protein" that FDA interpreted in its Final Rule, nor did it change the background statutory assumptions against which FDA developed its interpretation. From 2011 on, the public had ample opportunities to comment on the exact definition of "protein" that FDA adopted in the Final Rule, *see supra* Part I.A.4, and to raise the same argument Teva now makes, that the

[7] Teva does not challenge the omission of a definition for "chemically synthesized polypeptide" from the Final Rule on logical outgrowth grounds. Nor could it, as "'[o]ne logical outgrowth of a proposal is surely . . . to refrain from taking the proposed step.'" *Idaho Conservation League*, 930 F.3d at 508 (alteration and omission in original) (quoting *New York v. EPA*, 413 F.3d 3, 44 (D.C. Cir. 2005) (per curiam)).

definition "impermissibly favors naturally derived proteins over chemically synthesized ones," Pls.' Suppl. Br. at 9. Teva never availed itself of that opportunity, but FDA's decision to formalize the definition consistently set forth over the course of a decade sprung no unfair surprise on Teva or any other interested party.[8] As the federal defendants rightly observe, "[n]o divination was required on the part of interested parties to predict that that FDA might adopt the precise definition of the term 'protein' that it had proposed" over the course of nearly a decade. Fed. Defs.' Suppl. Br. at 11 (citing *Agape Church, Inc. v. FCC*, 738 F.3d 397, 411 (D.C. Cir. 2013)). Teva, like other interested parties, was afforded adequate notice of and multiple opportunities to comment on that definition before FDA issued its Final Rule. The 2019 Act's deletion of the analytically distinct term "chemically synthesized polypeptide" thus has no bearing on the procedural validity of FDA's longstanding interpretation of the term "protein."[9] The Final Rule, as a properly promulgated legislative rule, is owed *Chevron* deference.

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[8] In its comments on the exclusion of Copaxone from FDA's Preliminary List of products to be transitioned to BLAs, which were filed about two months after the enactment of the 2019 Act, Teva questioned FDA's application of the Final Rule to Copaxone, but did not challenge the Final Rule's definition of "protein" or assert any procedural impediment to the Final Rule. *See* AR at 1008–23. Teva raises these arguments for the first time in this litigation, and makes its procedural arguments partly in response to the Court's request for clarification of the procedural challenges alluded to by Teva in its opening briefs. Teva's requested relief for the alleged procedural violations, namely, vacatur of the Final Rule and remand to FDA with instructions to adopt Teva's preferred construction of the term "protein" and to classify Copaxone as a biologic, *see* Pls.' Suppl. Br. at 12–13, clearly overreaches. The remedy Teva proposes would be extraordinary, *see, e.g.*, *Hill Dermaceuticals, Inc. v. FDA*, 709 F.3d 44, 46 n.1 (D.C. Cir. 2013) (noting that relief for an APA violation should be "limited only to vacating the unlawful action, not precluding future agency decisionmaking"), and is poorly tailored to remediate the single decision of FDA, determining that Copaxone did not qualify as a "protein," that Teva challenges in its Complaint, *see* Compl. ¶¶ 75–89.

[9] Relying on the Supreme Court's decision in *Encino I*, Teva also contends that the Final Rule is also procedurally invalid because of "FDA's failure to address the current version of the statute" in issuing the Final Rule and that *Chevron* deference should be withheld on that ground. Pls.' Suppl. Br. at 3 (emphasis omitted); *see also id.* at 3–4 (citing *Encino I*, 136 S. Ct. at 2125); Pls.' Opp'n at 18–20. As an initial matter, Teva's argument relies on the premise that FDA developed its interpretation "by reference to characteristics of natural proteins" and therefore "should have reconsidered its definition," Pls.' Opp'n at 19 (emphasis omitted), a premise that, as explained *infra* Part III.B.2.a, is faulty. Further, *Encino I* denied *Chevron* deference, on procedural grounds, to a Department of Labor regulation reversing the agency's decades-old stance on a question of statutory interpretation. The Department had offered "barely any explanation" of its shift in policy in the challenged regulation. *Encino I*, 136 S. Ct. at 2126. As a result, the Court found that the regulation "was issued without the reasoned explanation that was required in light of the Department's change in position and the significant reliance interests involved" to survive arbitrary and capricious review under the APA and therefore "receive[d] no *Chevron* deference." *Id.* In contrast, here, FDA explained in detail the development of its interpretation of "protein" in numerous Guidance Documents,

2. FDA's Reasonable Interpretation of "Protein" Is Owed Deference

Teva next challenges the substance of the Final Rule, contending that FDA's interpretation of "protein" is contrary to section 351, such that the definition is "not in accordance with law," 5 U.S.C. § 706(2)(A), because it requires that molecules have a "specific, defined sequence" of amino acids to qualify as protein, *see* Pls.' Mem. at 20–26; Pls.' Opp'n at 18–26. This reading of the term, in Teva's view, imposes a distinction between chemically synthesized and naturally derived proteins that not only is foreclosed by the 2019 Act, but also is unreasonable. *See* Pls.' Mem. at 20–26; Pls.' Opp'n at 18–26. Defendants counter that the term "protein" unambiguously refers to substances with a "specific, defined sequence," *see, e.g.*, Fed. Defs.' Mem. at 21–24; Fed. Defs.' Reply at 14–17; Mylan Reply at 13–16; Mylan Suppl. Br. at 6–9, and, moreover, that, at a minimum, "protein" is sufficiently ambiguous to permit the agency's reasonable interpretation of the term as requiring a "specific, defined sequence," *see, e.g.*, Fed. Defs.' Mem. at 24–28; Mylan Mem. at 25–34; Sandoz Mem. at 27–35.

Under *Chevron*'s deferential standard, review of an agency's interpretation of a statute it administers proceeds in two steps. At Step One, the Court asks "whether Congress has directly spoken to the precise question at issue." *Chevron*, 467 U.S. at 842; *see also Cal. Cmtys. Against Toxics*, 928 F.3d at 1053. In making this determination, "using the traditional tools of statutory interpretation," courts "'examine the [statute's] text, structure, purpose, and legislative history to determine if the Congress has expressed its intent unambiguously.'" *Eagle Pharms., Inc. v.*

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its Proposed Rule, and its Final Rule. *See supra* Part I.A.4. Further, the Final Rule addressed the 2019 Act in describing FDA's decision not to finalize its definition of "chemically synthesized polypeptide" and in responding to related comments. *See supra* Part I.A.4.c. Whether those efforts are substantively sound is a separate question, discussed *infra* Part III.B.2, but they at least exceed the "minimal level of analysis" *Encino I* suggests is required for a regulation to pass procedural muster, especially where FDA has maintained, not reversed, its consistent interpretation of "protein." *Encino I*, 136 S. Ct. at 2125; *cf. Kiewit Power Constructors Co. v. Sec'y of Lab.*, 959 F.3d 381, 398–99 (D.C. Cir. 2020) (suggesting that *Encino I*'s lack of deference resulted primarily from "the Court's recognition that, under the circumstances, a cursory explanation was inadequate 'in particular because of decades of industry reliance on the Department's prior policy'") (quoting *Encino I*, 136 S. Ct. at 2126).

Azar, 952 F.3d 323, 330 (D.C. Cir. 2020) (alteration in original) (quoting *U.S. Sugar Corp. v. EPA*, 830 F.3d 579, 605 (D.C. Cir. 2016) (per curiam)). If the statute "is susceptible of 'only [one] possible interpretation,'" *Petit v. U.S. Dep't of Educ.*, 675 F.3d 769, 781 (D.C. Cir. 2012) (alteration in original) (quoting *Cnty. of L.A. v. Shalala*, 192 F.3d 1005, 1015 (D.C. Cir. 1999)), or "unambiguously forbids the Agency's interpretation," *Barnhart v. Walton*, 535 U.S. 212, 218 (2002); *see also Am. Hosp. Ass'n v. Azar*, 964 F.3d 1230, 1241 (D.C. Cir. 2020), the Court "must give effect to the unambiguously expressed intent of Congress," *Chevron*, 467 U.S. at 843; *see also NASDAQ Stock Market, LLC v. SEC*, 961 F.3d 421, 426 (D.C. Cir. 2020). If, however, the contested statute can be read in more than one way, may permit the agency's interpretation, or is silent as to the relevant question, the case moves to Step Two. *See Util. Air Regul. Grp. v. EPA* ("*UARG*"), 573 U.S. 302, 315 (2014); *Van Hollen, Jr. v. FEC*, 811 F.3d 486, 495 (D.C. Cir. 2016).

At Step Two, "the question for the court is whether the agency's answer is based on a permissible construction of the statute." *Chevron*, 467 U.S. at 843. In other words, the agency's statutory interpretation "must come within the zone of ambiguity the court has identified after employing all its interpretive tools." *Kisor v. Wilkie*, 139 S. Ct. 2400, 2416 (2019). In conducting this analysis, "[d]eference is due to the agency's permissible interpretation 'if the agency has offered a reasoned explanation for why it chose that interpretation.'" *Cal. Cmtys. Against Toxics*, 928 F.3d at 1055 (quoting *Vill. of Barrington v. Surface Transp. Bd.*, 636 F.3d 650, 660 (D.C. Cir. 2011)). This "is a requirement an agency can fail." *Kisor*, 139 S. Ct. at 2416.

(a) Chevron Step One

FDA declined to deem Teva's NDA for Copaxone an approved BLA pursuant to the BPCIA's transition provision because it determined that Copaxone does not have a "specific, defined sequence" of amino acids and therefore is not a "biological product" within the meaning of section 351. Thus, the "precise question at issue" is whether section 351 permits FDA to interpret "protein" to refer to a molecule that, among other features, has a "specific, defined sequence" of amino acids.[10] Both sides contend that their preferred response to this question prevails at Step One. Teva argues that FDA's interpretation fails because the 2019 Act "unambiguously forecloses an interpretation of 'protein' that rests on a distinction between natural proteins and synthetic ones." Pls.' Mem. at 22. In Teva's view, the "specific, defined sequence" requirement in FDA's definition does exactly that. *See id.* at 22–24; Pls.' Opp'n at 21–24. The federal defendants and Mylan counter that FDA's interpretation is not only permitted, but in fact compelled by the scientifically accepted plain meaning of the term "protein." Fed. Defs.' Mem. at 21; *see also id.* at 21–24; Fed. Defs.' Reply at 14–17; Mylan Mem. at 25 n.13; Mylan Reply at 15–16; Mylan Suppl. Br. at 6–9.[11]

Congress did not specifically define the term "protein" in either the BPCIA or the 2019 Act, an omission that presents an initial obstacle to the parties' Step One claims. *See* 42 U.S.C. § 262(i)(1); *Braeburn Inc.*, 389 F. Supp. 3d at 20 (finding that Step One "present[ed] a high hurdle" where the statute did not "'specifically define the phrase[]'" at issue) (second alteration in original) (quoting *Otsuka Pharm. Co. v. Burwell*, 302 F. Supp. 3d. 375, 394 (D.D.C. 2016),

[10] Teva does not challenge any other aspect of FDA's interpretation of protein, for example, the forty amino acid length requirement.

[11] Sandoz, in contrast to the federal defendants and Mylan, submits that "protein" is ambiguous and FDA's interpretation is properly evaluated at Step Two of the *Chevron* analysis. Sandoz Mem. at 27–29; Sandoz Reply at 13–15.

aff'd sub nom. Otsuka Pharm. Co. v. Price, 869 F.3d 987 (D.C. Cir. 2017))). A statutory definition is not required for the meaning of a term to be unambiguous. *See Petit*, 675 F.3d at 781 (citing *Nat. Res. Def. Council v. EPA*, 489 F.3d 1364, 1373 (D.C. Cir. 2007)). Here, however, the "traditional tools of statutory interpretation," *Eagle Pharms. Inc.*, 952 F.3d at 330, offer little to clarify the meaning of "protein" in section 351.

"In addressing a question of statutory interpretation, [courts] begin with the text." *City of Clarksville v. FERC*, 888 F.3d 477, 482 (D.C. Cir. 2018); *see also Eagle Pharms. Inc.*, 952 F.3d at 330 ("Of the tools of statutory interpretation, '[t]he most traditional tool, of course, is to read the text.'") (alteration in original) (quoting *Engine Mfrs. Ass'n v. EPA*, 88 F.3d 1075, 1088 (D.C. Cir. 1996))).[12] Generally, when a statutory term is undefined, courts look first to "that term's 'ordinary, contemporary, common meaning.'" *Food Mktg. Inst. v. Argus Leader Media*, 139 S. Ct. 2356, 2362 (2019) (quoting *Perrin v. United States*, 444 U.S. 37, 42 (1979)); *see also Bd. of Cnty. Comm'rs v. Fed. Housing Fin. Agency*, 754 F.3d 1025, 1028–29 (D.C. Cir. 2014) ("[W]here a statute's terms are undefined, our interpretation is guided by the terms' 'regular usage.'") (quoting *Lopez v. Gonzales*, 549 U.S. 47, 53 (2006)). Ordinary meaning is of limited utility, however, when determining the proper interpretation of a scientific term employed by Congress in the context of "a complex statutory regime, laden with scientific language and other terms of art," such as the PHSA. *ViroPharma, Inc. v. Hamburg*, 898 F. Supp. 2d 1, 19 (D.D.C. 2012) (citing *Emerson v. Steffen*, 959 F.2d 119, 121 (8th Cir. 1992)); *cf.* AR at 294 n.12 (noting that "[n]on-scientific references are not particularly helpful in defining" the term "protein"). In

[12] The remaining "traditional tools of statutory interpretation" are not particularly illuminating. The legislative history does not give any insight into Congress's intended meaning of "protein." Congress's original inclusion, and subsequent deletion, of the parenthetical exception provides some structural evidence that Congress intended for "protein" to encompass both naturally derived and chemically synthesized molecules, as appropriate, but otherwise sheds little light on either the characteristics that Congress considered essential to "proteins" or the scope of the protein category. Nor does the stated purpose of the BPCIA, to establish "a biosimilars pathway balancing innovation and consumer interests," BPCIA § 7001(b), help to answer the precise question at hand.

such cases, courts may look instead to the "plain and established meanings" of the relevant terms "in scientific and regulatory parlance." *Abbott Lab'ys. v. Young*, 920 F.2d 984, 992 (D.C. Cir. 1990); *see also FAA v. Cooper*, 566 U.S. 284, 292 (2012) ("[I]t is a 'cardinal rule of statutory construction' that, when Congress employs a term of art, 'it presumably knows and adopts the cluster of ideas that were attached to each borrowed word in the body of learning from which it was taken.'") (quoting *Molzof v. United States*, 502 U.S. 301, 307 (1992)); *T-Mobile S., LLC v. City of Roswell*, 574 U.S. 293, 301 (2015) (same); *McDermott Int'l, Inc. v. Wilander*, 498 U.S. 337, 342 (2001) ("In the absence of contrary indication, we assume that when a statute uses such a term [of art], Congress intended it to have its established meaning."); *Loving v. IRS*, 742 F.3d 1013, 1017 (D.C. Cir. 2014) (seeking to identify, at *Chevron* Step One, "any specialized meaning that people in the field attach to" the statutory term being construed).

Relying on this principle of statutory interpretation, defendants contend that FDA's interpretation prevails at Step One because the "plain and established meaning" of "protein" in the scientific community unambiguously indicates that all "proteins," regardless of how they are made, have a "specific, defined sequence." Fed. Defs.' Mem. at 21–24. In support of this argument, they cite to a number of scientific sources reviewed by FDA during its rulemaking process, *see id.* at 22–23 (citing sources); Mylan Reply at 15–16 (same).[13] As Teva points out,

[13] *See also, e.g.*, AR at 812, Michael D. Larrañaga et al., *Hawley's Condensed Chemical Dictionary* 1145 (16th ed. 2016) (defining "protein" as "[a] complex, high polymer containing carbon, hydrogen, oxygen, nitrogen, and usually sulfur, and composed of chains of amino acids connected by peptide linkages" and noting that "[t]he sequence of amino acids . . . is of critical importance in genetics"); *id.* at 817, *A Dictionary of Science* 666 (6th ed. 2010) ("Protein molecules consist of one or several long chains . . . of amino acids in a characteristic sequence."); *id.* at 831, Thomas E. Creighton, *Encyclopedia of Molecular Biology* (1999) ("The amino acid sequence defines the order of the side chains throughout the [protein]."); *id.* at 839, Jeremy M. Berg et al., *Biochemistry* 53 (5th ed. 2002) ("The striking fact is that each protein has a unique, precisely defined amino acid sequence." (emphasis omitted)); *id.* at 846, Thomas D. Pollard & William C. Earnshaw, *Cell Biology* 21 (2002) ("Proteins consist of one or more linear polymers called polypeptides, which consist of various combinations of 20 different amino acids . . . linked together by peptide bonds . . . The sequence of amino acids in each type of polypeptide is unique." (emphasis omitted)); *id.* at 858, Harvey Lodish et al., *Molecular Cell Biology* 66 (6th ed. 2007) ("The primary structure of a protein is simply the linear arrangement, or sequence, of the amino acid residues that compose it."); *id.* at 869, Bruce Alberts et al., *Molecular Biology of the Cell* 129 (4th ed. 2002) ("Each type of protein has a unique sequence of

however, a closer look at the record evidence reveals that, while the sources defendants cite in their briefing indeed reference a specific or characteristic sequence in their definitions or descriptions of "protein," not all scientific sources FDA consulted appear to include that requirement, though none reject or otherwise contest it. *See* Pls.' Opp'n at 21–24.[14]

Mylan suggests that the "silence" of these sources does not show ambiguity or "undermine Congress'[s] intent in having the general scientific understanding of the term [protein] apply." Mylan Reply at 16. Congress likely did intend for "protein" to carry its usual scientific meaning, but the discrepancy in the literature does not provide, for the non-expert reader, sufficient, unambiguous evidence of that scientific meaning to answer the precise question at hand at Step One. Defendants appear to acknowledge this flaw in their argument, encouraging the Court to rely not only on the literature, but also on the fact that "FDA found that the scientific community understood that a 'protein' has a 'specific, defined sequence' of amino acid." *Id.* This push towards deference to the agency's scientific evaluation to prove the meaning of a statutory term itself shows that defendants cannot prevail at Step One. In the absence of unambiguous scientific agreement, the identification of a scientific consensus around the "specific, defined sequence" requirement "is the kind of highly technical, specialized interstitial matter that Congress often does not decide itself, but delegates to specialized

amino acids, exactly the same from one molecule to the next. Many thousands of different proteins are known, each with its own particular amino acid sequence."); *id.* at 297 n.33 (quoting *Encyclopedia of Molecular Biology* 2037 (1994)) ("'[T]he arrangement of amino acid residues in the primary structure of a protein is not random, but is precisely determined by the genetic information stored in the chromosomal DNA or RNA.'").

[14] *See also, e.g.*, AR at 820, J. Stenesh, *Dictionary of Biochemistry and Molecular Biology* 387 (2d ed. 1989) (defining a "protein" as "[a] high molecular weight polypeptide of L-amino acids that is synthesized by living cells" and describing proteins as "biopolymers with a wide range of molecular weights, structural complexity, and functional properties"); *id.* at 825, *American Heritage Science Dictionary* 507 (2005) (defining "protein" as "[a]ny of a large class of complex organic chemical compounds that are essential for life[,] . . . consist of long chains of amino acids connected by peptide bonds and have distinct and varied three-dimensional structures"); *id.* at 296 ("'Proteins are molecules that consist of one or more polypeptide chains. These polypeptides range in length from ~40 to over 4000 amino acid residues.'") (quoting Donald Voet & Judith G. Voet, *Biochemistry* 62 (3d ed. 2004)).

agencies," not to courts, "to decide." *Zuni Pub. Sch. Dist. No. 89 v. Dep't of Educ.*, 550 U.S. 81, 90 (2007). Whether FDA acted reasonably in carrying out this delegation is a question to be answered at Step Two, not Step One.

Nor, however, is FDA's determination that a "specific, defined sequence" is an essential characteristic of a protein unambiguously foreclosed by the statute, as Teva submits. In support of this theory, Teva argues that Congress's deletion of the parenthetical exception for "chemically synthesized polypeptides" in the 2019 Act prohibits FDA from imposing "an interpretation of 'protein' that rests on a distinction between natural proteins and synthetic ones." Pls.' Mem. at 22; *see also* Pls.' Opp'n at 21–24. This argument fundamentally misunderstands both the text of section 351 and FDA's interpretation: contrary to Teva's representations, neither the statute nor the rule ever distinguished between naturally derived and chemically synthesized proteins. Before the 2019 Act was passed, section 351 categorized *all* "proteins," whether naturally derived or chemically synthesized, as biological products, except for "chemically synthesized *polypeptides*." 42 U.S.C. § 262(i)(1) (2012) (emphasis added). The use of these different terms in the statue signaled that the excluded "polypeptides" were necessarily a distinct subset of molecules within the broader group of "proteins," differentiated on some basis other than method of manufacture, with respect to which the unmodified term protein was apparently agnostic. *See, e.g.*, *Henson v. Santander Consumer USA Inc.*, 137 S. Ct. 1718, 1723 (2017) ("[W]hen we're engaged in the business of interpreting statutes we presume differences in language . . . convey differences in meaning.").

The parenthetical exclusion thus did not separate naturally derived proteins from chemically synthesized proteins, as Teva now argues. Rather, it treated all qualifying molecules as proteins, regardless of mode of manufacture, except for the subset of "chemically synthesized

polypeptides" set out in the exception. The divide, then, was between "proteins," whether natural or synthetic, and "chemically synthesized polypeptides." By deleting the exception in the 2019 Act, Congress did not foreclose a distinction between naturally derived and chemically synthesized proteins present in the earlier version of section 351; that distinction never existed. Instead, it eliminated the carve-out to the general rule of treatment as proteins for previously excluded molecules.

Moreover, standing alone, FDA's interpretation does not differentiate between natural and synthetic proteins in the manner Teva suggests. The agency, placing appropriate weight on Congress's initial decision to use the term "polypeptide" rather than "protein" in the parenthetical exception, recognized that the relevant distinction was between those two types of molecules, not between differently made types of proteins. *See, e.g.*, AR at 306–07, 804, 1027; *id.* at 307 ("[T]here seems to be no basis in the legislative history of the [BPCIA] to support a finding of Congressional intent to regulate all chemically synthesized proteins . . . as drugs under the [FDCA]" rather than as biologics under the PHSA.). Thus, from 2011 on, its definition of protein was meant to apply to both naturally derived and chemically synthesized proteins. In the Final Rule, FDA explained that "all amino acid polymers that meet FDA's interpretation of the term 'protein'" *id.* at 1026, would be treated as such, "irrespective of the method of manufacture." *Id.* at 1027; *see also id.* at 307 (same). As further evidence that the interpretation treats natural and synthetic proteins on equal terms, FDA, applying its definition, transitioned a number of chemically synthesized proteins, including some that had previously been excluded as chemically synthesized polypeptides, to BLAs. *See id.* at 1143–51. Even if the 2019 Act imposed the restriction that Teva suggests, that limitation would not unambiguously foreclose

FDA's interpretation, which, on its face, does not discriminate between natural and synthetic proteins.

The term "protein" is thus ambiguous with respect to the "specific, defined sequence" requirement, which is neither compelled nor foreclosed by the text of section 351. Therefore, analysis proceeds to Step Two.

(b) Chevron Step Two

At Step Two, FDA's interpretation of "protein" survives only if the agency reasonably construed the statutory language, a standard that the agency can fail. *Kisor*, 139 S. Ct. at 2416. To satisfy *Chevron*'s second inquiry, an agency must supply a reasonable explanation of "how [its] interpretation serves the statute's objectives." *Mako Commc'ns, LLC v. FCC*, 835 F.3d 146, 150 (D.C. Cir. 2016) (internal quotation omitted). Review at this step is "highly deferential," *Vill. of Barrington*, 636 F.3d at 665 (internal quotation omitted), with "'[p]articular deference . . . given by the court to an agency with regard to scientific matters in its area of technical expertise,'" *Ctr. for Biological Diversity v. EPA*, 749 F.3d 1079, 1088 (D.C. Cir. 2014) (quoting *Nat'l Wildlife Fed'n v. EPA*, 286 F.3d 554, 560 (D.C. Cir. 2002)). In cases that touch upon complex scientific issues, the court "'must look at the decision not as the chemist, biologist or statistician that [it is] qualified neither by training nor experience to be,'" *id.* at 1087–88 (quoting *Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976) (en banc)), but instead "aims only to discern whether the agency's evaluation was rational," *id.* at 1088 (quoting *Nat. Res. Def. Council v. EPA*, 824 F.2d 1211, 1216 (D.C. Cir. 1987)).

As the Final Rule and Proposed Rule articulate, FDA interprets the term "protein" as found in section 351 to refer only to molecules that, in addition to meeting the other criteria set forth in the agency's definition, have a "specific, defined sequence" of amino acids. AR at 802–

03, 1025. This interpretation falls within the range of scientifically accepted meanings of "protein," as described above, *see supra* Part III.B.2.a, and therefore, in the absence of a statutory definition, within the "zone of ambiguity" invoked by Congress's use of "protein," a scientific term of art. *See Barnhart*, 535 U.S. at 218. The agency developed this definition after convening a working group of experts to analyze the term "protein," surveying the relevant scientific literature, considering various scientific, regulatory, and statutory factors, and engaging with the regulated industry for nearly a decade. *See supra* Part I.A.4. FDA proffered, in great detail, a reasonable explanation of its interpretation in the 2011 Memorandum, stood by that explanation in each of its Guidance Documents, and reiterated it in the Proposed Rule. *Id.*

In particular, FDA has consistently emphasized and expanded upon its view, based on scientific expertise, that the term "protein refers to chains containing a specific, defined sequence of amino acids." AR at 803 (emphasis omitted); *see also, e.g.*, *id.* at 297. The agency appears to have surveyed scientific literature related to both natural and synthetic proteins and determined that, in light of the key role amino acid sequences play in the production and function of proteins in nature, a "specific, defined sequence" was an essential characteristic of proteins. It next concluded that this characteristic was shared by synthetic proteins, which are modeled on their natural predecessors. As a result of these scientific conclusions, FDA decided to interpret the term "protein" to encompass a "specific, defined sequence" requirement. This analytic process is itself rational, and, in light of the broad scientific agreement that proteins have a specific, defined sequence of amino acids, described *supra* Part III.B.2.a, so too is the definition it produced.

Nonetheless, Teva contends that FDA's interpretation is unreasonable for three main reasons, none of which is persuasive. First, Teva argues that, in the wake of the 2019 Act,

"'proteins' previously excluded as 'chemically synthesized polypeptides'" must be treated as biological products, such that interpretations that distinguish between natural and synthetic proteins are now unreasonable under the statute. Pls.' Mem. at 25. It claims that the specific, defined sequence requirement does exactly that. This argument rests, again, on two faulty premises that before the enactment of the 2019 Act, section 351, as amended by the BPCIA, excluded chemically synthesized proteins rather than chemically synthesized polypeptides, and also that FDA's interpretation of "protein" in the Guidance Documents and Proposed Rule likewise excluded chemically synthesized proteins. As explained above, these characterizations of both section 351 and FDA's rulemaking process are inaccurate. *See supra* Part III.B.2.a.

Second, Teva submits that FDA derived the "specific, defined sequence" criterion solely from an examination of naturally derived proteins and related scientific literature and, as a result, that requirement "is no longer justified as a starting point for the definition of 'protein.'" Pls.' Mem. at 25. The administrative record clearly shows otherwise, however. FDA examined sources related to both natural and synthetic proteins in developing the "specific, defined sequence" requirement.[15] The scientific literature reviewed by FDA strongly, if not unambiguously, reflects a consensus view that proteins have a specific, defined sequence of amino acids. *See supra* Part III.B.2.a. This characteristic is therefore an essential feature of any protein, central to its design and efficacy as a therapeutic product. As the sources explain, in nature, "proteins are made by living organisms" from a DNA template, which "has a specific, defined sequence." Fed. Defs.' Mem. at 23 (citing J.A., William K. Purves et al., *Life: The Science of Biology* 218–20 (6th ed. 2000), ECF No. 46-4). The "DNA template is used to create an RNA template, which is then used to build a protein." *Id.* (citing Purves et al., *supra*, at 218–

[15] *See, e.g.*, AR at 812, Larrañaga et al., *supra*, at 1145 ("Some proteins have been synthesized[.]"); *id.* at 817, *A Dictionary of Science*, *supra*, at 666; *id.* at 820, Stenesh, *supra*, at 387.

20). "The specific, defined sequence is passed on each step" and is therefore "an inherent property endowed by the way organisms make proteins." *Id.* (citing Purves et al., *supra*, at 220–21). The sequence of a protein also determines its structure, which in turn determines its function in living organisms, including humans. *See, e.g.*, AR at 856–57, Lodish et al., *supra*, at 64–65 ("A key concept in understanding how proteins work is that function is derived from three-dimensional structure, and three-dimensional structure . . . is specified by amino acid sequence." (emphasis omitted)).

FDA determined, after reviewing the scientific literature, that a specific, defined sequence is characteristic of both natural and synthetic proteins. *See, e.g.*, *id.* at 297, 803. Teva correctly notes that the requirement in scientific writing appears to have originated from observations about natural proteins, *see* Pls.' Mem. at 25, but that fact alone does not render FDA's application of this attribute to synthetic proteins unreasonable. While proteins can now be synthesized in a laboratory, they originated in nature, and it was with regard to natural proteins that this category of molecules was first researched and described. *See* Fed. Defs.' Mem. at 25–26. Further, the amino acid sequence dictates the function of synthetic proteins just as it does for their natural equivalents. *See, e.g.*, J.A., Raushan K. Singh et al., *Protein Engineering Approaches in the Post-Genomic* Era, 19 Current Protein & Peptide Sci. 5, 5 (2018). It is thus unsurprising that FDA identified in the scientific literature a consensus that synthetic proteins, as more recent additions to the protein family, share this fundamental quality of the naturally derived proteins on which they are modeled, among other common defining properties. *See supra* Part III.B.2.a; Fed. Defs.' Mem. at 25–26. Put simply, as FDA reasonably concluded, molecules that do not have a specific, defined sequence are not regarded as proteins in the scientific community, regardless of how they are made. *See* Fed. Defs.' Mem. at 26. Indeed, for

FDA to find that chemically synthesized proteins need not share a characteristic that the agency, in reliance on scientific expertise, has identified as a defining trait of the category would deprive the term "protein" of all set meaning.

Further, the "specific, defined sequence" requirement does not operate to exclude all chemically synthesized molecules from the protein category, as Teva implies. Under FDA's interpretation, backed by the scientific expertise of the agency and of the sources on which it relied, chemically synthesized polymers without a specific, defined sequence are not proteins; chemically synthesized polymers with a specific, defined sequences are. The record indicates that several viable methods of manufacturing synthetic proteins, with the requisite specific, defined sequence, exist. *See, e.g.*, J.A., Stephen B.H. Kent, *Total Chemical Synthesis of Proteins*, 38 Chem. Soc. Rev. 338, 339–41 (2009) (describing "modern methods for the total chemical synthesis of proteins" with defined amino acid sequences); *id.*, Jeffrey A. Borgia & Gregg B. Fields, *Chemical Synthesis of Proteins*, 18 Tibtech 243, 243–49 (2000) (listing "three general chemical approaches to constructing proteins" with specific amino acid sequences); AR at 306 & n.60 (citing Kent, *supra*, at 338). Indeed, FDA applied its interpretation to transition at least three chemically synthesized proteins from NDAs to BLAs. *See* AR at 1125, 1130, 1132.

Finally, Teva contends that the "specific, defined sequence" requirement "uniquely burdens chemically synthesized proteins, because any naturally derived protein with a 'DNA/RNA templated source' gets a free pass." Pls.' Mem. at 25–26 (quoting AR at 1121); *see also* AR at 803 (noting that, for naturally derived molecules, a "specific, defined sequence" is "generally provided by a corresponding DNA or RNA sequence").[16] Teva's theory is that the

[16] In support of this theory, Teva points to FDA's classification of Vitrase, a naturally derived product, compared to its treatment of Copaxone and to a statement in FDA's Decision Memorandum, finding that Copaxone is not a protein, that "[s]ynthetic proteins are generated by the stepwise addition of specific amino acids in a defined sequence." AR at 1120; *see also* Pls.' Mem. at 26–27. These specific arguments challenge FDA's interpretation or

Final Rule treats natural and synthetic proteins unevenly because naturally derived proteins are assumed to have a specific, defined sequence latent in the DNA/RNA template from which they are made, while manufacturers of chemically synthesized polymers must show that their products in fact meet the requirement. The Final Rule in fact holds natural and synthetic proteins equally to the standard of having a specific, defined amino acid sequence. That makers of synthetic proteins must do more to demonstrate that this standard is met does not prove the standard is either, as Teva contends, "weighted . . . toward recognizing natural proteins," Pls.' Opp'n at 26, or unreasonable. Instead, this is simply indicative of the scientific reality that naturally derived proteins are known to have specific, defined sequences, while chemically synthesized polymers may have this essential trait, but alternatively may have a random sequence that disqualifies them from classification as proteins.

Teva next contends that, by imposing this further showing on manufacturers of synthetic products, "FDA has acted unreasonably to 'frustrate the policy that Congress sought to implement'" in the 2019 Act. Pls.' Opp'n at 24 (quoting *Shays v. FEC*, 528 F.3d 914, 925 (D.C. Cir. 2008)). This argument relies on the unsubstantiated assumption that Congress intended in the 2019 Act to "eliminat[e] any process-based distinction for determining whether to regulate a complex polypeptide product as a biologic." Pls.' Opp'n at 25–26. Teva argues that, because manufacturers of chemically synthesized polymers may show that their products have a specific, defined sequence by providing information about how they are made, the specific, defined sequence requirement assures that only polymers made through certain methods will be classified as proteins. Setting aside the question of whether the 2019 Act in fact reflects any such congressional intent, Teva overlooks the fact that the "specific, defined sequence"

application of the Final Rule, not the statutory interpretation set forth in the Final Rule, and therefore are not properly evaluated under *Chevron*.

requirement is not a process-based requirement. It is a requirement that natural and synthetic products alike exhibit a fundamental characteristic shared by all proteins before being classified as such. Though certain methods of manufacture may reliably result in specific, defined sequences and others (among them the process used by Teva to manufacture Copaxone) will not, the requirement itself is a reasonable effort by FDA to ensure that the category "protein" is restricted to molecules truly fitting the scientific consensus regarding that definition.

If anything, the 2019 Act reflects Congress's continuing use of the word "protein," a term of art with an accepted scientific meaning, and its accompanying intent that FDA discern and apply that scientific meaning. FDA did so, determining that all "proteins" have a specific, defined sequence of amino acids. Teva's contention that only some chemical processes will generate proteins under FDA's interpretation, if true, does not render the interpretation unreasonable. It merely reflects a limitation inherent in the term selected by Congress and reasonably construed by FDA. In short, the "specific, defined sequence" requirement is a reasonable construction of the term "protein" in section 351. It is neither unattainable nor, on its face, unduly burdensome for chemically synthesized molecules. FDA's interpretation is therefore owed deference under *Chevron*.

C. FDA's Determination That Copaxone Is Not a "Protein" Is Not Arbitrary and Capricious

Teva next argues that FDA's application of the Final Rule to Copaxone, and conclusion in the Decision Memorandum that Copaxone is not a protein, was arbitrary and capricious. The law is well-settled that an agency action "is arbitrary and capricious if (1) the agency 'has relied on factors which Congress has not intended it to consider'; (2) the agency 'entirely failed to consider an important aspect of the problem'; (3) the agency's explanation 'runs counter to the evidence before the agency'; or (4) the explanation 'is so implausible that it could not be

ascribed to a difference in view or the product of agency expertise.'" *Am. Bankers Ass'n v. Nat'l Credit Union Admin.*, 934 F.3d 649, 663 (D.C. Cir. 2019) (quoting *Motor Vehicles Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Ins. Co.* ("*State Farm*"), 463 U.S. 29, 43 (1983)). "Agency action is also arbitrary and capricious if it 'offered insufficient reasons for treating similar situations differently.'" *Cal. Cmtys. Against Toxics*, 928 F.3d at 1057 (quoting *Transactive Corp. v. United States*, 91 F.3d 232, 237 (D.C. Cir. 1996)).

Under the arbitrary and capricious standard, the "scope of review is 'narrow,'" considering "only whether the [agency] examined 'the relevant data' and articulated 'a satisfactory explanation' for [its] decision, 'including a rational connection between the facts found and the choice made.'" *Dep't of Commerce v. New York*, 139 S. Ct. 2551, 2569 (2019) (quoting *State Farm*, 463 U.S. at 43). The court "'may not substitute [its] own judgment for that' of the agency." *Am. Bankers Ass'n*, 934 F.3d at 663 (quoting *FERC v. Elec. Power Supply Ass'n*, 136 S. Ct. 760, 782 (2016)). Of particular relevance here, "[i]n the context of a challenge to the FDA's decisionmaking, [courts] 'give[] a high level of deference' to the agency's scientific analysis of the evidence before it, and must avoid 'unduly second-guess[ing] [those] scientific judgments.'" *Pharm. Mfg. Rsch. Servs., Inc. v. FDA*, 957 F.3d 254, 262 (D.C. Cir. 2020) (third, fourth, and fifth alterations in original) (first quoting *Rempfer v. Sharfstein*, 583 F.3d 860, 867 (D.C. Cir. 2009); and then quoting *Cytori Therapeutics, Inc. v. FDA*, 715 F.3d 922, 923 (D.C. Cir. 2013)).

Applying these standards to the present case, FDA acted reasonably and in accordance with applicable law in finding that Copaxone is not a protein and in declining to transition Copaxone to a BLA on that basis. Implementing the Final Rule's definition of "protein," FDA concluded in its Decision Memorandum that Copaxone did not satisfy the "specific, defined

sequence" requirement and therefore was not a "protein." AR at 1120–21. In response to Teva's comments to the docket regarding the Preliminary List, the agency explained that the "specific, defined sequence" requirement "describes the manner in which specific amino acids are added to a polymer in a defined sequence," following a pre-defined template that results in an identical sequence across batches. *Id.* at 1120. Natural proteins are produced from "a DNA template," "the existence of [which] renders the sequence 'specific and defined,'" and allows FDA to determine that molecules have a specific, defined sequence based solely on their natural origins. *Id.* Synthetic proteins share this quality because of "the stepwise addition of specific amino acids in a defined sequence" during synthesis, which provides a manmade template for their production. *Id.*

Copaxone, however, is not made through this predictable process, but rather through "reaction chemistry," which generates recurring but not identical or pre-defined results across batches. *Id.*; *see also supra* Part I.B.1. Indeed, Teva has acknowledged that, far from being dictated by a predetermined template, Copaxone's amino acid sequences are "determined during the chemical solution polymerization process." AR at 184; *see also id.* at 478, 484. As a result, FDA determined that "'there is a negligible likelihood of having identical amino acid sequences along entire copolymer chains from batch to batch,'" *id.* at 1121 (quoting *id.* at 708), and Copaxone exhibits "sequence variability," *id.* at 1120. FDA acknowledged that some "[c]onserved [i.e., replicated] sequences" occur in glatiramer acetate products like Copaxone, but noted that they are "limited to short amino acid sequences within the copolymer chain." *Id.* at 1121 (quoting *id.* at 708). This minimal degree of specificity, FDA concluded, did not meet the "specific, defined sequence" standard.

In so reasoning, FDA appears to have considered the appropriate scientific factors and to have provided a rational distinction between Copaxone and bona fide proteins, whether natural or synthetic. Teva does not point to any scientific evidence in the record indicating that Copaxone can meet the standard of specificity FDA outlined. Nonetheless, Teva challenges FDA's reasoning as arbitrary and capricious on two grounds: Teva regards FDA's findings, set forth in its Decision Memorandum, as inconsistent with respect to, first, FDA's treatment of other therapeutic products and, second, FDA's prior finding that Copaxone is sufficiently well-defined for the agency to approve generic glatiramer acetate products. As explained below, neither criticism is persuasive.

First, Teva argues that the Decision Memorandum applied a heightened specificity standard to Copaxone compared to the standard imposed on Vitrase and Creon, two products that Teva alleges "are less well characterized than Copaxone, and whose active ingredients may vary from batch to batch" but were nonetheless transitioned to BLAs. Pls.' Mem. at 27; *see also id.* at 27–32; Pls.' Opp'n at 27–31. Vitrase and Creon are naturally derived compounds, sourced from animal tissues, that consist of multiple naturally derived proteins. AR at 799, 1107. FDA responded to this critique, leveled by Teva in its comments on the Preliminary List, in the Decision Memorandum. The agency wrote that, although the sequences of the discrete proteins that make up Vitrase and Creon are not "fully characterize[ed]," FDA can determine that each of the proteins has a specific, defined sequence because they are naturally derived and thus have an "inherent DNA/RNA templated source." *Id.* at 1121. Contrary to Teva's characterization of FDA's treatment of Vitrase and Creon as allowing these products to "ignore [the specific, defined sequence] requirement entirely" because they are naturally derived, Pls.' Mem. at 28, FDA has reasonably explained that Vitrase and Creon in fact satisfy the requirement precisely

because they are naturally derived. Though Teva contends that the lack of "characterization" means that the molecules in Vitrase and Creon lack specific, defined sequences, Pls.' Mem. at 29 (quoting AR at 9), in fact, the term indicates only that science has not yet been able to identify the exact sequences, not that they do not exist, *see* Fed. Defs.' Mem. at 31.

Teva doubles down on the FDA's purported inconsistent treatment of Vitrase and Creon, maintaining that FDA found that Vitrase and Creon have specific and defined sequences despite their molecular variation, while Copaxone, which has sequence variation but not molecular variation, does not. Pls.' Mem. at 29–31; Pls.' Opp'n at 27–30. FDA acknowledged the variability of Vitrase and Creon, writing, with respect to Vitrase, that "the amino acid sequence of [Vitrase] molecules varies based both on the species and the tissue from which they are sourced . . . [and] the amino acid sequence for [Vitrase] enzymes extracted from a particular type of tissue from the same species may vary." AR at 1121 (quoting *id.* at 10). The key variation here is not, as Teva would have it, a variation in the sequence of different batches of the same type of protein molecule, but rather variation in the types of protein molecules in different batches, with a single type of protein molecule having the same sequence across every batch that includes it. *See id.* at 10 (explaining that Vitrase and similar products may contain "a single type of . . . molecule" or "multiple types of . . . molecules"). As Sandoz helpfully puts it, "this simply means that, for example, one batch may contain a mixture of 'HYAL1' and 'HYAL2,' while another batch may contain a mixture of 'HYAL1,' 'HYAL2' and 'HYAL3.' But . . . the sequence of 'HYAL1' is always the same, and the sequence of 'HYAL2' is always the same, even though 'HYAL1' and 'HYAL2' have different sequences because they are different proteins." Sandoz Mem. at 38.[17]

[17] Teva additionally argues that, because each batch of Creon and Vitrase contains a different mix of molecules, their treatment as proteins is inconsistent with FDA's interpretive premise that a "specific, defined

Drawing on this scientific backdrop, FDA concluded that because "each of the sequences is specific and defined for a given species and source," Vitrase and Creon met the specific, defined sequence requirement because each individual protein molecule in the mixture has an identical amino acid sequence across batches, even if a particular molecule is not present in every batch. AR at 1121. Contrast Copaxone, a product consisting of a single type of molecule which, by Teva's own calculations, has anywhere between 10^{12} (one trillion) to 10^{29} (a trillion times a trillion) possible sequences. *See id.* at 479. Faced with this staggering potential for variation across entire copolymer chains, FDA reasonably concluded that the short replicated sequences between batches of glatiramer acetate do not give Copaxone a "specific, defined sequence" as a whole. *See id.* at 1121.[18] Teva challenges the scientific premises underlying this conclusion, *see* Pls.' Mem. at 29–31, but "[m]eaningful review" in this context "does not require [the court] to step into the FDA's shoes and reassess its scientific judgments—a role that [courts] are 'ill-equipped' to play 'under the guise of the APA's arbitrary and capricious standard.'" *Pharm. Mfg. Rsch. Servs., Inc.*, 957 F.3d at 265 (quoting *Cytori Therapeutics*, 715 F.3d at 927). FDA's determination that Copaxone, a product consisting of a single type of molecule with nearly infinite possible sequences, does not have a specific, defined sequence and therefore is not

sequence" is essential to a "protein" "because sequence specificity is what gives proteins their structure and their structure determines their function." Pls.' Opp'n at 28. In fact, FDA rejected an interpretation of "protein" that relied on function during its rulemaking because some proteins perform functions that are also carried out by non-protein molecules. *See* AR at 300; Fed. Defs.' Reply at 18–19. Rather, the "specific, defined sequence" requirement ensures the characteristic molecular consistency of proteins, which Vitrase and Creon exhibit within discrete types of molecules, while the very heterogeneity of Copaxone molecules is thought to contribute to its "clinical efficacy," AR at 27, 71–72.

[18] Nor does Teva's contention that Vitrase and Creon exhibit "broader sequence variability" than Copaxone, Pls.' Mem. at 29, hold weight. In contrast to the trillions of possible sequences of Copaxone, the record evidence, at best, supports the inference that Creon has "possibly hundred of different enzyme variants," AR at 1018 n.74, *see also id.* at 1101, and Vitrase, which consists of a single family of proteins, likely far fewer, *id.* at 799, perhaps between two and seven, *see id.* at 10 & n.10 (citing sources). Further, the relevant variation, under FDA's test, is not molecular diversity, which is the type of variation that Vitrase and Creon have, but sequence variation across different samples of the same molecule. As explained above, FDA has determined that each type of molecule included in batches of Vitrase and Creon has the same sequence across batches.

a protein is not inconsistent with its determination that Vitrase and Creon, compounds made of multiple molecules that all have a specific, defined sequence, are proteins.

Teva next argues that FDA's determination that Copaxone lacks a "specific, defined sequence" is inconsistent with its finding that Copaxone is sufficiently well-defined for the agency to approve, in the FDCA context, generic glatiramer acetate products. Pls.' Mem. at 32–36; Pls.' Opp'n at 31–33. Under the FDCA, to make the requisite showing that a generic version of a reference listed drug is "safe and effective," an ANDA applicant must demonstrate, among other factors, that the generic drug is "identical in active ingredient(s)" to the reference listed drug. 21 C.F.R. § 314.92(a)(1); *see also* 21 U.S.C. § 355(j)(2)(A)(ii), (iii); *supra* Part I.A.1. In its letter denying Teva's eighth and final Citizen Petition, FDA explained that "[c]urrent analytical techniques are capable of supporting a demonstration of active ingredient sameness between the generic glatiramer acetate injection and [Copaxone]," AR at 727; *see also id.* at 727–31, and explained that ANDA applicants are able to show "that the molecular identity and diversity of [generic] glatiramer acetate is equivalent to that of the active ingredient in Copaxone," *id.* at 739; *see also supra* Part I.B.2. It articulated criteria for evaluating the "sameness" of generic glatiramer acetate products, which included replication of the "batch-to-batch variation" exhibited by Copaxone, AR at 718 n.69, and the "fundamental reaction scheme" used by Teva to manufacture its product, *id.* at 718–19; *see also supra* Part I.B.2. By preserving the "propagational shift" that is characteristic of Copaxone, FDA concluded, generic products would contain similar "conserved aspects" (that is, replicated amino acid sequences) to those present in Copaxone, which are thought to contribute to its therapeutic effects. AR at 718–19.

Teva now submits that this determination reflects a finding by FDA "that the active ingredient [in Copaxone], glatiramer acetate, has amino acid sequences that are sufficiently well

defined, such that the ANDA applicant can demonstrate" active ingredient sameness. Pls.' Mem. at 32–33; *see also* Pls.' Opp'n at 31–33.[19] This argument conflates requirements and standards under two completely different statutes that FDA has interpreted and applied in completely different contexts. The active-ingredient sameness criterion derives from the text of the FDCA and FDA's regulations interpreting and applying that criterion to the approval of generic drugs. The "specific, defined sequence" stems from the inclusion of "proteins" in the PHSA's definition of "biological products" and FDA's resulting regulations. The FDCA requirement seeks to determine whether different therapeutic products will have an equivalent therapeutic effect, while the PHSA requirement seeks to accurately classify therapeutic products in order to determine how they should be regulated. Nor was FDA's sameness standard for glatiramer acetate products based solely on the presence or absence of replicated sequences. Rather, the agency set forth four factors, and a forty-three page guide, through which to evaluate glatiramer acetate products, which included the replicated sequences as one consideration and the batch-to-batch variation inherent to Copaxone as another. *See id.* at 700, 697–739; *supra* Part I.B.2.

Further, FDA's assessment that Copaxone's short, conserved sequences are capable of replication in generic glatiramer acetate products, and its determination that those sequences should be considered when approving generics, is in no way equivalent to a finding that Copaxone molecules as a whole have the "specific, defined sequence" characteristic of proteins.

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[19] Though Teva raised this argument in its comments to the Preliminary List, *see* AR at 1015–16, FDA did not specifically respond to it in the Decision Memorandum, *see id.* at 1117–23. FDA did, however, rely on its letter denying Teva's eighth Citizen Petition in the Decision Memorandum. That letter addressed at length the agency's determinations both that Copaxone lacks a "specific, defined sequence" and that generic glatiramer acetate products could be approved, *see id.* at 708, 716–26, and the Decision Memorandum explicitly incorporated its key conclusion that "'[a]lthough [Copaxone's] preserved local sequences may be reflected in analyses used to establish active ingredient sameness, there is also broader sequence variability inherent to Copaxone. As such, glatiramer acetate is best described not as a protein, but rather as a heterogeneous mixture of copolymers,'" *id.* at 1121 (quoting AR at 708). Thus, the Decision Memorandum may be fairly construed to have "invoked" the grounds articulated in the letter. *Regents*, 140 S. Ct. at 1907 (internal quotation omitted).

FDA has consistently found that the sequences of the four amino acids in Copaxone are "neither entirely conserved (i.e., replicated) from batch to batch . . . nor completely random." AR at 706–07; *see also, e.g.*, *id.* at 1121. In the Decision Memorandum, as Teva acknowledges, FDA explained that Copaxone has "preserved local sequences" that can be "used to establish active ingredient sameness," but also exhibits "broader sequence variability" that precluded the agency from finding that it has the "specific, defined sequence" requisite for classification as a protein. *Id.* at 1121 (quoting *id.* at 708). This explanation for why FDA evaluates Copaxone's limited identical sequences differently under different standards appears rational: FDA's interpretation of "protein" requires complete sequential identity across molecules, while its understanding of active ingredient sameness requires only sufficient identity to ensure that a generic product is safe and therapeutically effective.[20]

Teva nonetheless persists in attempting to link the two standards, insisting that "the considerations overlap in substance" and that "both the active-ingredient-sameness and 'specific, defined sequence' inquiries turn on the chemical makeup of the product in question." Pls.' Opp'n at 31–32. As the federal defendants point out, however, FDA has never tied its active-ingredient-sameness determinations and its interpretation of "protein" together. *See* Fed. Defs.' Reply at 19–20. To the contrary, FDA made a stray observation in the 2011 Memorandum that protein products might find it "more difficult" to demonstrate active ingredient sameness,

[20] The FDA's treatment of Vitrase is fully consistent with this explanation, rather than, as Teva contends, inconsistent. *See* Pls.' Mem. at 34–35. Vitrase's situation is the inverse of Copaxone's: while FDA has transitioned Vitrase from a "drug" to a "protein," it did not approve ANDAs for generic equivalents when Vitrase was classified as a drug because Vitrase's active ingredient "ha[d] not yet been sufficiently characterized" to allow FDA to determine that a generic product had the same active ingredient. AR at 16 n.20. As explained above, FDA has reasonably concluded that the various molecules in Vitrase, as naturally derived proteins, have specific and defined sequences by virtue of their inherent DNA/RNA templates, even if those sequences remain unknown to researchers. In contrast, active ingredient "sameness" determinations require at least some detailed understanding of the active ingredient in order for FDA to determine whether it is present in generic products. FDA's conclusion that Vitrase satisfies one statutory standard but not the other is neither irrational nor inconsistent with its treatment of Copaxone.

implicitly recognizing that the standard for qualifying as a protein differs from FDA's test for active ingredient sameness under the FDCA. AR at 298; *see also id.* at 298–99. Though Teva is correct that amino acid sequence is relevant to both inquiries, FDA has explained that the "protein" analysis centers on whether a molecule has a "specific and defined," as opposed to a "random" sequence, while the active-ingredient-sameness analysis generally considers the molecular diversity and composition of a product, and looks to amino acid sequences as part of that evaluation. *See id.* at 717–27. That FDA has answered these two questions differently with respect to the same product reflects the differences in the standards, not any inconsistent or arbitrary treatment of the product.

In short, FDA examined the relevant scientific factors, considered the whole record and Teva's objections, and proffered a reasonable explanation for its decision that Copaxone is not a "protein." The APA requires nothing more.

D. FDA's Determination That Copaxone Is Not "Analogous" to a Protein Was Reasonable

In a last-ditch effort to obtain relief, Teva challenges FDA's interpretation of section 351's category of products "analogous" to proteins, set forth only in the Decision Memorandum, as foreclosed by the statute, and FDA's application of the "analogous product" provision to Copaxone as arbitrary and capricious. *See* Pls.' Mem. at 35–43; Pls.' Opp'n at 34–43. Neither challenge has merit.[21]

[21] Teva further argues, in the alternative, that Copaxone is a biological product that should be deemed "analogous" to a vaccine. *See* Pls.' Mem. at 39–40; Pls.' Opp'n at 34–35, 41–42. This argument fails because Teva has not exhausted its administrative remedies with respect to that theory, which was raised for the first time in Teva's comments on the docket regarding the Preliminary List. *See* AR at 1021–22. "[T]he APA requires exhaustion of administrative remedies ' . . . when expressly required by statute or . . . an agency rule.'" *L. Xia v. Tillerson*, 865 F.3d 643, 658 (D.C. Cir. 2017) (second omission in original) (quoting *Darby v. Cisneros*, 509 U.S. 137, 154 (1993)). FDA regulations clearly mandate that "[a] request that the Commissioner take or refrain from taking any form of administrative action must first be the subject of a final administrative decision based on a [Citizen Petition] . . . before any legal action is filed in a court complaining of the action or failure to act[.]" 21 C.F.R. § 10.45(b). Teva did not contend that Copaxone was analogous to a vaccine in any of the eight Citizen

FDA has not published a legislative rule or guidance document defining the "analogous product" category with respect to products "analogous" to proteins. *See, e.g.*, AR at 1028 ("A definition of products that are 'analogous' to a 'protein' for purposes of section 351(i)(1) of the [PHSA] is outside the scope of this rulemaking."). Due to this omission, Teva argues that FDA "has no claim to deference regarding its application of the statutory phrase to Copaxone." Pls.' Mem. at 37; *see also* Pls.' Opp'n at 35–37. FDA has, however, tacitly interpreted the phrase in both the Final Rule, which observes "that it would not be appropriate for the statutory term 'analogous product' to be interpreted in a way that would include products that are specifically excluded by this final rule," AR at 1028, and the Decision Memorandum, which states that "it would not be appropriate to interpret the statutory term 'analogous product' (with reference to 'protein') in a way that would include amino acid polymers that are specifically excluded by the interpretation of the term 'protein' set forth in FDA's . . . Final Rule," *id.* at 1121.

Moreover, in the Decision Memorandum, FDA wrote, in the course of applying the "analogous product" provision to Copaxone, that it "would not consider an amino acid polymer that does not have a specific, defined sequence to be 'analogous' to a protein." *Id.* In contrast, the agency regards substances, including mixtures, that are comprised at least in part of a protein with a specific, defined sequence, as products "analogous" to proteins, even if "the protein

Petitions it filed. It now claims that inclusion of this contention in its comments on the docket regarding the Preliminary List suffices to meet the exhaustion requirement because that docket was meant to address "'questions about FDA's interpretation of the 'transition' provision'" of the BPCIA, without limitation. Pls.' Opp'n at 42 (quoting AR at 874). Raising a question about the transition provision's application to Copaxone is not, however, equivalent to a formal request for FDA to classify Copaxone as a product "analogous" to a vaccine, particularly since that category of biological products long predates the BPCIA, and was in fact in place when Teva filed its initial NDA for Copaxone in 1995. *See* 42 U.S.C. § 262(a) (1994). Before its comments on the Preliminary List, Teva never asserted, in any forum, that Copaxone was "analogous" to a vaccine, despite ample opportunity, and an obligation, to do so before filing suit on that ground. As a result, this argument may not properly be considered here. *See, e.g.*, *Ass'n of Am. Physicians & Surgeons, Inc. v. FDA*, 358 F. App'x 179, 180–81 (D.C. Cir. 2009) (declining to review claims brought by petitioners who failed to file a Citizen Petition as required by 21 C.F.R. § 10.45(b)).

component(s) is [sic] present in low levels or unknown amounts." *Id.* at 1122 n.16.[22] These statements, though not interpretations set forth in a legislative rule or other document specifically meant to interpret the "analogous product" provision, are interpretations nonetheless. Whether FDA has sufficiently supported its interpretation of the "analogous product" provision to require that products "analogous" to "proteins" have a "specific, defined sequence" of amino acids is a separate question, assessed below.

Agreeing that FDA has provided an interpretation of the "analogous product" provision, defendants urge that *Chevron* should apply. *See* Fed. Defs.' Mem. at 39; Mylan Mem. at 38–39; Sandoz Mem. at 42–44; Fed. Defs.' Reply at 20–21; Mylan Reply at 21–22; Sandoz Reply at 21–23. Courts in this Circuit "routine[ly] . . . analyze APA claims that arise out of the FDA's letter-decision interpretations of the FDCA" under that standard. *Otsuka Pharm. Co.*, 302 F. Supp. 3d at 389; *see also AstraZeneca Pharms. LP v. FDA*, 713 F.3d 1134, 1139 (D.C. Cir. 2013) (applying *Chevron* to FDA's letter decision interpreting the FDCA); *Mylan Lab'ys., Inc. v. Thompson*, 389 F.3d 1272, 1279–80 (D.C. Cir. 2004) (same, collecting cases); *Braeburn Inc.*, 389 F. Supp. 3d at 19 ("*Chevron*'s framework applies to an FDA interpretation of the FDCA set forth in a letter decision."). This extension of *Chevron* deference to FDA's informal interpretations of the FDCA stems from "the complexity of the statutory regime under which the FDA operates, the FDA's expertise [and] the careful craft of the [regulatory] scheme" FDA "devised to reconcile the various . . . provisions" of the statutes it administers. *Mylan Lab'ys., Inc.*, 389 F.3d at 1280, logic that applies with equal force to FDA's letter interpretations of the PHSA, as a second highly technical statute the agency administers.

[22] This portion of FDA's interpretation was explained in greater detail in a March 18, 2020 memorandum, written by FDA's Biological Product Classification Subcommittee, that set out recommendations on determining whether "certain combination products and naturally derived mixtures" should be transitioned to BLAs, including as products analogous to proteins. *See* AR at 1084–96.

Applying *Chevron*'s two-step framework, *see supra* Part III.B.2, to FDA's limited interpretation of the "analogous product" provision indicates that FDA's construction is reasonable, though not well-defined or well-explained beyond its response to the precise question at hand, of whether a product "analogous" to a "protein" must have a "specific, defined sequence" of amino acids. Teva contends that the "analogous product" provision creates a "residual" category, Pls.' Mem. at 35, meant to classify as biological products some products that are not proteins, and that the statute unambiguously indicates, at *Chevron* Step One, that the critical shared quality of proteins and products analogous to them is the ability "to induce or modulate an immune response in the body," *id.* at 38. Defendants counter that the term "analogous" is ambiguous and that, at *Chevron* Step Two, FDA's determination that the critical "analogous" quality is a "specific, defined sequence" of amino acids is reasonable. *See* Fed. Defs.' Mem. at 39–42; Mylan Mem. at 39–41; Sandoz Mem. at 42–44; Fed. Defs.' Reply at 20–24; Mylan Reply at 21–24; Sandoz Reply at 21–25.

At Step One, the parties agree both that the "analogous product" provision, as applied to proteins, brings certain non-protein products into the biological product category and that the term "analogous," standing alone, indicates that products within the purview of this provision must share some defining features with proteins, but does not suggest what those qualities might be. *See, e.g.*, Pls.' Mem. at 35–37; Fed. Defs.' Mem. at 39–41. Teva nonetheless submits that its preferred interpretation of the provision, that "analogous" products are those that "induce or modulate an immune response," is unambiguously compelled by legislative history and statutory structure, while FDA's interpretation is unambiguously foreclosed. Pls.' Mem. at 37–39; Pls.' Opp'n at 37–39.

In support of this theory, Teva relies on *Blank v. United States*, 400 F.2d 302 (5th Cir. 1968), a decades-old case that was specifically overruled by Congress, *see* Heart Disease, Cancer, Stroke, and Kidney Disease Amendments of 1970, Pub. L. No. 91-515, § 291, 84 Stat. 1297, 1308 (1970); Pls.' Mem. at 37–38; Pls.' Opp'n at 38–39. The *Blank* Court, construing the original 1902 version of section 351, determined that, because the types of biological products listed in that statute were all "immunological agents," analogous products must share the defining feature of being used for immunological purposes. 400 F.2d at 304. The federal defendants offer persuasive evidence that Congress rejected this construction of the "analogous products" provision in its 1970 amendments to section 351, *see* Fed. Defs.' Mem. at 43–44 (citing H.R. Rep. No. 91-1035 (1970) at 1–2 ("The provisions of the bill are in the nature of emergency legislation necessitated by [the *Blank* decision].")), though Teva contests this characterization of the legislative history, *see* Pls.' Opp'n at 38–39. Regardless, even if *Blank*'s reasoning remains relevant to other categories of biological products, the record makes plain that "proteins," which were added to section 351 decades after *Blank* was decided and carry out a multitude of different functions in the body, are not all "immunological agents," *see, e.g.*, AR at 798, 1107; *see also id.* at 869, Alberts et al., *supra*, at 129 (noting that proteins "execute nearly all cell functions"), which is one of the reasons that FDA avoided a functional definition of "protein" in the first place, *see id.* at 300. The defining feature of this category, for the purpose of identifying analogous products, cannot be a characteristic that is not shared by all proteins.

Teva next points to FDA's regulations construing the "analogous product" provision with respect to other types of biological products, arguing that these interpretations "all focus on whether a product shares the same immunological function and basic building blocks as the enumerated biologic." Pls.' Mem. at 38; *see also id.* at 38–39 (citing sections of 21 C.F.R.

§ 600.3(h)(5)). Only one of the regulatory definitions of "analogous product" FDA has published incorporates an "immunological function" criterion.[23] If anything, the diverse factors in the definitions suggest that "analogous product" takes on a meaning appropriate to each category it modifies, rather than a one-size-fits-all approach.[24] Moreover, FDA's construction of the statutory phrase in relation to other products has no bearing on whether the phrase itself has an unambiguous meaning with respect to the precise question at issue here at Step One.

Finally, Teva contends that FDA's interpretation that a product "analogous" to a protein must have a "specific, defined sequence" is foreclosed by the statute because this effectively means that "if a product is not a 'protein' under FDA's regulatory definition, it cannot be 'analogous' to a protein either." Pls.' Mem. at 41. As a result, in Teva's view, FDA has impermissibly "read[] the 'analogous product' category out of the statute as applied to proteins." *Id.*; *see also id.* at 41–43; Pls.' Opp'n at 35–37. The category of products "analogous" to

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[23] *See* 21 C.F.R. § 600.3(h)(5)(i) (A product is analogous "[t]o a 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) (A product is analogous "[t]o a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or amino acid, derived from whole blood, plasma, or serum."); *id.* § 600.3(h)(5)(iii) (A product is analogous "[t]o a toxin or antitoxin, if 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.").

[24] Teva contends that this adaptable approach to the "analogous product" phrase itself "'violate[s] [a] rule of statutory construction'" that "'a single use of a statutory phrase must have a fixed meaning across a statute.'" Pls.' Opp'n at 36 (alterations in original) (quoting *Lomax v. Ortiz-Marquez*, 140 S. Ct. 1721, 1725 (2020) (explaining the interpretive canon that the meaning of a word or phrase that appears in different provisions of a single statute should generally hold constant within the statute)). Likewise, Teva attempts to apply the *ejusdem generis* canon in support of its preferred interpretation, which, it claims, appropriately "interpret[s] (and cabin[s]) a general phrase . . . that appears at the end of a list." Pls.' Opp'n at 38 (citing *Circuit City Stores, Inc. v. Adams*, 532 U.S. 105, 115 (2001)). This strained effort, which, as Teva would have it, results in a reading of "analogous product" to require that products "share the same immunological function and basic building blocks as the enumerated biologic," *id.*, encounters the obstacle described above, that not all proteins have immunological functions. Further, the interpretive canon that "'[t]he words of a statute must be read in their context and with a view to their place in the overall statutory scheme,'" *Sierra Club v. Wheeler*, 956 F.3d 612, 616 (D.C. Cir. 2020) (quoting *UARG*, 573 U.S. at 320), supports a construction of "analogous product," as a residual phrase that encompasses products "analogous" to any of nine distinct types of biological products, that captures products that are "analogous" to the enumerated types of products in category-specific ways. In any event, because the referent qualities of "analogous" are ambiguous regardless of whether the term has a uniform or a category-specific meaning, this dispute about the import of canons of construction need not be resolved.

"proteins" is not, however, a null set under FDA's construction, as evidenced by the fact that the agency has identified at least some mixtures with protein components in this category. *See* AR at 1084–97. It is simply restricted to products that, although they may not satisfy the criteria to be a "protein" in other respects, have the characteristic "specific, defined sequence" of amino acids. 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. As to the specifics, the phrase is ambiguous and therefore cannot foreclose FDA's selection of the "specific, defined sequence" requirement as the touchstone. Teva's arguments to the contrary notwithstanding, the question of which characteristics render a product "analogous" to a protein is left to FDA's determination, and is assessed at *Chevron* Step Two.

At Step Two, FDA's interpretation of the "analogous product" provision need only be reasonable to merit deference. "The analysis of disputed agency action under *Chevron* Step Two and arbitrary and capricious review is often 'the same, because under *Chevron* step two, [the court asks] whether an agency interpretation is arbitrary or capricious in substance.'" *Agape Church, Inc.*, 738 F.3d at 410 (alteration in original) (quoting *Judulang v. Holder*, 565 U.S. 42, 52 n.7 (2011)). Such is the case here, where Teva's challenge to FDA's specific determination that Copaxone is not "analogous" to a protein rests on the alleged invalidity of FDA's interpretation itself, not on the premise that Copaxone in fact satisfies the "specific, defined sequence" requirement. *See* Pls.' Mem at 41–44; Pls. Opp'n at 35–37, 39–41.[25]

[25] Even if Teva did challenge FDA's application of its interpretation to Copaxone on this ground, it would fail for the reasons explained *supra* Part III.C. Teva contends instead that Copaxone is an "analogous product" because it satisfies the criteria Teva proposes for identifying such products. *See* Pls.' Mem. at 39–41. Since the Court does not adopt Teva's preferred interpretation, these arguments need not be addressed.

FDA stated in its Decision Memorandum that Copaxone was not regarded as "analogous" to a protein because the agency "would not consider an amino acid polymer that does not have a specific, defined sequence to be 'analogous' to a protein," as substances "that fail to meet a specific category in the definition of 'biological product' because they are specifically excluded from that category" cannot be considered "analogous" biological products. AR at 1121. Defendants argue that this finding reflects a reasoned determination by FDA that a specific, defined amino acid sequence "is a fundamental property of proteins" and that "[c]onsequently, a product cannot be analogous to a protein if it does not share this fundamental, defining property." Fed. Defs.' Mem. at 41; *see also* Mylan Mem. at 39–41; Sandoz Mem. at 43–44. As explained above, *see supra* Part III.B.2.b, FDA's conclusion that a "specific, defined sequence" is a definitional characteristic of proteins is reasonable.

Teva challenges the extension of this conclusion to analogous products on two grounds. First, it argues that "the entire point of the 'analogous product' category" is to regulate as biological products some substances that "do not fall squarely within any of the enumerated categories." Pls.' Mem. at 41 (emphasis omitted). That premise is true as far as it goes, but does not indicate how FDA should determine whether a product stands outside of the enumerated categories but is similar enough to be regulated as a biological product nonetheless. FDA's stance, that a product cannot fail entirely to meet one of the agency's definitional criteria for a category of biological products yet nonetheless become a biological product, offers a reasonable method by which to distinguish sufficiently similar products from products that are too distinct to be considered analogous. The agency appears to understand the "analogous product" category as a narrow residual provision meant to accommodate products that satisfy the regulatory

definitions of each category in most, if not all, regards, but are not an exact fit for whatever reason.

In the case of products "analogous" to proteins, for example, FDA has identified one such reason, that a product may "include one or more identified biological product component(s) (e.g., protein), as well as one or more non-biological product component(s) . . . that can contribute to the product's activity." AR at 1089. These products contain a protein with a specific defined sequence and therefore are not "specifically excluded" by FDA's definition of protein, but because they contain an additional, non-protein component, nor are they a perfect match for the protein category. *Id.* at 1094. They are "analogous" to proteins because their protein components are "necessary . . . to achieving the intended therapeutic effect," but they are not simply "proteins" because their non-biological product components also contribute to their efficacy. *Id.* FDA's approach to these products expands the set of proteins and protein-like substances that qualify as "biological products" beyond the fixed "protein" category, but also ensures that the category retains some fixed, scientifically valid meaning. In contrast, FDA has determined that Copaxone does not contain any component with a "specific, defined sequence." To consider a substance that does not satisfy this fundamental requirement "analogous" to a protein would be to stretch the set of protein and protein-like products considered "biological products" beyond the range that FDA has found to be scientifically and interpretively sound.

Teva next argues that FDA's interpretation must fail "because it provides no standard for deciding whether a product is 'analogous' to a protein." Pls.' Opp'n at 41. As a general matter, Teva is correct. FDA has not provided a comprehensive definition or standard for identifying products analogous to proteins. The *Chevron* inquiry, however, is trained on the "precise question at issue," which, here, is the narrow question of whether a product "analogous" to a

protein must have a specific, defined sequence. As to that discrete prong of the overall analogous product analysis, FDA has answered yes. The standard is apparent from the requirement itself.

FDA's scientific judgment that a "specific, defined sequence" is an essential enough feature of proteins that it must be shared even by "analogous" products is thus a reasonable interpretation of the "analogous product" provision. At a minimum, given the ambiguity of the term "analogous" standing alone, FDA's choice of the "specific, defined sequence" criterion as the determining factor is a rational one. Other options, including the alternative construction suggested by Teva, might offer equally viable or even better interpretations, but a reviewing court, "'[i]n an area characterized by scientific and technological uncertainty, . . . must proceed with particular caution, avoiding all temptation to direct the agency in a choice between rational alternatives.'" *Oceana, Inc. v. Ross,* 920 F.3d 855, 864 (D.C. Cir. 2019) (quoting *Am. Wildlands v. Kempthorne,* 530 F.3d 991, 1000 (D.C. Cir. 2008)). FDA did not err in formulating its interpretation or in applying it to determine that Copaxone is not "analogous" to a protein.

Teva's arguments, in short, all rest on the same premise: that FDA should have formulated an approach to defining and identifying proteins and analogous products that would have resulted in Copaxone's classification as a biological product. The agency's failure to reach Teva's preferred outcome does not, however, indicate that it acted unreasonably, arbitrarily, or capriciously.[26]

[26] If FDA's interpretation were not subject to *Chevron* deference, it would be evaluated instead under the somewhat less deferential standard set forth in *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944), which would afford the interpretation "'respect' . . . but only to the extent that [it] ha[s] the 'power to persuade,'" *Orton Motor, Inc. v. U.S. Dep't of Health & Hum. Servs.*, 884 F.3d 1205, 1211 (D.C. Cir. 2018) (omission in original) (quoting *Christensen v. Harris Cty.*, 529 U.S. 576, 587 (2000)). Given the highly technical nature of the interpretive question at issue and FDA's expertise in this area, the result would likely be the same.

IV. CONCLUSION

For the foregoing reasons, Teva's Motion for Summary Judgment, ECF No. 31, is denied; and the cross-motions for summary judgment filed by the federal defendants, ECF No. 36, Mylan, ECF No. 34, and Sandoz, ECF No. 38, are granted.

An Order consistent with this Memorandum Opinion will be entered contemporaneously.

Date: December 31, 2020

BERYL A. HOWELL
Chief Judge