February 19, 2020

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2015-D-4750 - The "Deemed to be a License" Provision of the BPCI Act: Questions and Answers – Draft Guidance for Industry; Preliminary List of Approved NDAs for Biological Products That Will Be Deemed To Be BLAs on March 23, 2020

Dear Sir or Madam:

Teva Pharmaceuticals USA, Inc. ("Teva") appreciates the opportunity to submit these comments regarding *The "Deemed to be a License" Provision of the BPCI Act: Questions and Answers – Draft Guidance for Industry* and *The Preliminary List of Approved NDAs for Biological Products That Will Be Deemed To Be BLAs on March 23, 2020*. Specifically, Teva submits that its product COPAXONE® (glatiramer acetate injection) falls squarely within the statutory definition of "biological product," and its approved New Drug Application ("NDA") for COPAXONE should therefore be deemed to be a license under section 351 of the Public Health Service Act.

I. Background

The Food and Drug Administration ("FDA" or the "Agency") has historically approved biological products and non-biological products under two distinct pathways. Biological products are approved pursuant to section 351 of the Public Health Service Act ("PHSA"), while non-biological products are approved under section 505 of the Federal Food, Drug, and Cosmetic Act ("FDCA"). COPAXONE was approved on December 20, 1996, pursuant to an NDA filed under section 505 of the FDCA. At that time, the products regulated under section 351 of the PHSA were limited to "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)."[1]

On March 23, 2010, Congress adopted the Biologics Price Competition and Innovation Act of 2009 ("BPCIA").[2] One provision of the BPCIA broadened the scope of "biological product" to include a "protein (except any chemically synthesized polypeptide)."[3] The definition of "biological product" was recently broadened even further by the Further Consolidated Appropriations Act, 2020 ("2020

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1 42 U.S.C. § 262(a) (1994). In 1997, Congress created a definition of the term "biological product" encompassing those same categories. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 123, 111 Stat. 2296, 2323-24 (1997) (adding PHSA § 351(i), 42 U.S.C. § 262(i)).

2 Pub. L. No. 111-148, tit. VII, subtit. A, 124 Stat. 804 (2010).

3 *Id.* § 7002(b), 124 Stat. at 814.

Act")[4] by eliminating the exclusion of "chemically synthesized polypeptides," such that "biological products" now encompasses all "proteins," including chemically synthesized polypeptides.[5]

Another provision of the BPCIA provides for the transition of certain previously approved drugs into the regulatory scheme for biological products. As of March 23, 2020, ten years after the BPCIA's enactment, for any "biological product" that was approved under section 505 of the FDCA, that approval shall be "deemed to be a license" under section 351 of the PHSA.[6]

The FDA has published a list of approved NDAs for drug products that are now considered "biological products" and hence will be "deemed to be a license" under section 351 of the PHSA as of March 23, 2020.[7] COPAXONE is noticeably absent from this list. Teva respectfully requests that the FDA correct this oversight, because COPAXONE falls squarely within the definition of a "biological product." COPAXONE therefore should be included on the list of biological products whose NDA approvals will be deemed to be a license under section 351 of the PHSA.

II. The FDA's Interpretation of "Protein"

Following enactment of the BPCIA, the PHSA's statutory definition of "biological product" included:

> 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.[8]

In order to implement this amended definition and clarify the scope of products that would now be regulated as "biological products," the FDA issued guidances setting forth its interpretation of the newly added term, "protein (except any chemically synthesized polypeptide)." Specifically, the FDA defined "protein" to mean "any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size."[9] The FDA also defined the term "chemically synthesized polypeptide" to mean "any amino acid polymer that (1) is made entirely by chemical synthesis; and (2)

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4 Pub. L. No. 116-94, 133 Stat. 2534 (2019).

5 *Id.* § 605, 133 Stat. at 3127.

6 BPCIA § 7002(e)(4)(A), 124 Stat. at 817, *as amended by* 2020 Act, § 607(1), 133 Stat. at 3127-3128.

7 Preliminary List of Approved NDAs for Biological Products That Will Be Deemed to be BLAs on March 23, 2020 (current as of December 31, 2019), fda.gov/media/119229/download.

8 42 U.S.C. § 262(i)(1) (2012).

9 U.S. Food & Drug Admin., *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* at 12-13 (2012); U.S. Food & Drug Admin., *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2) – Guidance for Industry* at 12-14 (2018), https://www.fda.gov/media/119278/download.

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is greater than 40 amino acids but less than 100 amino acids in size."[10] The FDA also issued a proposed rule to amend its regulations to incorporate these definitions.[11]

In adopting these definitions, the FDA explained that "proteins," "peptides," and "polypeptides" all refer to amino acid polymers made up of alpha amino acids linked by peptide bonds.[12] The FDA sought to distinguish "proteins" from "peptides," because "to the extent there is a generally accepted meaning of 'protein,' peptides appear to be outside the scope of this term," and therefore "*biological product* would not include peptides."[13] As between these terms, the FDA explained that "*peptide* generally refers to smaller, simpler chains of amino acids, while *protein* is used to refer to longer, more complex chains."[14] In order to provide a "scientifically reasonable, bright-line rule that provides regulatory clarity and facilitates the implementation of the BPCI Act," the FDA determined that "proteins" would be differentiated from "peptides" based on "a single, well-defined criteria": the length of the amino acid chain.[15] The FDA "concluded that a threshold of 40 amino acids is appropriate for defining the upper size boundary of a peptide" because "amino acid polymers that are greater than 40 amino acids may often assume several of the structural and functional characteristics that are generally associated with proteins, lending a higher level of complexity to these products."[16]

While the FDA noted the generally-accepted size-based distinction between "protein" and "peptide," there was no such recognized difference between "protein" and "polypeptide." Rather, the FDA acknowledged that scientific literature typically equated the two terms or at least considered "polypeptide" to be a subset within the scope of the term "protein."[17] However, the FDA explained that "[a]s amended by the BPCI Act, the term 'protein' specifically excludes chemically synthesized polypeptides."[18] In order to ensnare as broad a scope of compounds as reasonably possible within the statutory definition of "biological product," the FDA sought to define the "chemically synthesized polypeptide" exclusion narrowly.[19]

Noting that some scientific literature limits the size of "polypeptides" to those polymers having fewer than 100 amino acids, the FDA incorporated this size limit into the excluded category of

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10 *Id.*

11 Definition of the Term "Biological Product," 83 Fed. Reg. 63,817 (2018).

12 *Id*. at 63,820.

13 *Id*.

14 *Id*.

15 *Id*. ("This approach reflects the Agency's conclusion that, other than size, there does not appear to be a precise set of structural or functional attributes that would define a protein so as to clearly distinguish proteins from peptides."); *see also id.* at 63,821 ("FDA is proposing to codify an approach that distinguishes proteins from peptides based solely on size").

16 *Id*. at 63,821.

17 *Id*. at 63,820. The FDA cited Alberts, *Molecular Biology of the Cell* 129, 135 (4th ed. 2002) ("Proteins are therefore also known as polypeptides."), and Voet, *Biochemistry* 68 (3d ed. 2004) ("Proteins are molecules that consist of one or more polypeptide chains.").

18 *Id*. at 63,821.

19 *Id*.

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"chemically synthesized polypeptides," explaining that "FDA believes that any chemically synthesized polypeptide composed of more than 99 amino acids would have, among other characteristics, a level of structural and functional complexity and sensitivity to environmental conditions that makes regulating such a protein under the same statutory authority as the majority of proteins more appropriate."[20] Accordingly, "larger and/or more complex proteins (*i.e.*, amino acid polymers composed of more than 99 amino acids) are considered to be biological products regardless of their method of manufacture."[21] In other words, amino acid polymers of a certain length (*i.e.*, those having more than 99 amino acids) were "proteins" whether or not they are chemically synthesized, while those having between 40 and 99 amino acids were also "proteins" unless they fell into the express statutory exclusion for chemically synthesized products.

In sum, the FDA's interpretive guidance demonstrates that if it were not for the exclusion, there would be no such thing as a "polypeptide" that is not a "protein" and, hence, a "biological product." The FDA expressly relied upon scientific references equating the terms "protein" and "polypeptide." And more specifically, the FDA understood that ***any*** "chemically synthesized polypeptide" was a "protein," and tailored the definition of "chemically synthesized polypeptide" narrowly to allow "larger and/or more complex proteins" to nevertheless be "considered biological products regardless of their method of manufacture," while smaller, less complex proteins would be excluded to the extent made by chemical synthesis. The only reason why *all* "chemically synthesized polypeptides" were not regulated as biological products was the statutory exclusion.

As discussed above, the statutory exclusion of "chemically synthesized polypeptides" has now been eliminated by the 2020 Act. Accordingly, the "chemically synthesized polypeptides" that the FDA carefully carved out of "biological products" now fall within the scope of the term "protein," and must be regulated as "biological products."

III. COPAXONE Background

A. Chemistry of COPAXONE

COPAXONE was approved under section 505 of the FDCA in 1996 – well before the BPCIA expanded the definition of "biological product" to include a "protein."[22] COPAXONE's active ingredient is glatiramer acetate, a complex mixture of synthetic polypeptides containing four different amino acids – L-glutamic acid, L-alanine, L-tyrosine, and L-lysine.[23] While the individual polypeptides within the glatiramer acetate mixture differ in terms of size and sequence, the overall average molar fraction of each amino acid is well defined – *i.e.*, 0.141 L-glutamic acid, 0.427 L-alanine, 0.095 L-tyrosine, and 0.338 L-lysine, respectively – as is the overall average molecular weight of 5,000 to 9,000

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20 *Id*.

21 *Id*.

22 COPAXONE Prescribing Information at 1 (Dec. 2019), https://www.copaxone.com/globalassets/copaxone/prescribing-information.pdf.

23 *Id*. at 12.

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daltons.[24] The average length of these polypeptides is 40 to 100 amino acids.[25] Thus, glatiramer acetate comprises a complex mixture of polypeptides having an overall standardized size and proportion of amino acids.

Glatiramer acetate is made by chemical synthesis, and its preparation involves two primary steps: polymerization and partial depolymerization.[26] First, a solution of the specified proportion of each of the four amino acids (in their activated, N-carboxyanhydride forms) is prepared.[27] A pre-specified amount of an initiator is added to this solution, which starts the polymerization process.[28] Each molecule of the initiator binds to one of the activated amino acids.[29] Each initiator molecule thus serves as the C-terminus of a single growing polymer, while the amino acid serves as the N-terminus end.[30] Additional activated amino acids are sequentially added to the N-terminus end of each of the growing polymers until the amino acids have been consumed.[31]

Next, the polymers generated in the first step are cleaved to reduce their size and obtain the specified average molecular weight, noted above.[32] The cleavage reaction breaks the bond between two of the amino acids in a polymer chain, thus resulting in two, smaller chains without rearranging the relative positions of the amino acids in those chains.[33] The resulting mixture of alpha amino acid polymer chains is glatiramer acetate.[34]

While this synthetic process yields a mixture of polymers of varying length and sequence, neither the length nor the amino acid sequence is randomly generated; they are in fact dictated by the reaction mixture composition and conditions.[35] For example, the number and length of polymers in the pre-cleavage mixture are dependent upon the relative amount of initiator as compared to the amounts of amino acids.[36] As another example, the sequence in which amino acids are added to each polymer is a function of the relative reactivity and concentration of each of the amino acids.[37] Generally speaking,

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24 *Id*.

25 Matteo Caporro, *Two Decades of Subcutaneous Glatiramer Acetate Injection: Current Role of the Standard Dose, and New High-Dose Low-Frequency Glatiramer Acetate in Relapsing-Remitting Multiple Sclerosis Treatment*, 8 Patient Preference and Adherence 1123, 1124 (2014) ("Caporro").

26 FDA Response to Teva's Citizen Petition (Docket No. FDA-2015-P-1050) at 12-20 (Apr. 16, 2015).

27 *Id*. at 13-14.

28 *Id*.

29 *Id*. at 14.

30 *Id*. at 14-15.

31 *Id*. at 15.

32 *Id*. at 18.

33 *Id*.

34 *Id*.

35 *Id*. at 14-17.

36 *Id*. at 14-15.

37 *Id*. at 16-17.

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the more reactive and more highly concentrated an amino acid is in the solution, the sooner it will be added to the growing polymer.[38] Because the relative concentrations of the amino acids change as the polymerization proceeds and more reactive/concentrated species are consumed, the likelihood of a particular amino acid being added to each polymer varies down the length of each chain.[39] Thus, for example, alanine, being the most reactive and highly concentrated of the amino acids when the polymerization reaction commences, is preferentially incorporated into the growing polymer chains closer to the C-terminus initiator, while tyrosine, the least reactive and least concentrated amino acid, is preferentially incorporated closer to the N-terminus of each polymer.[40] This phenomenon is known as propagational shift, and, because the manufacturing process for making COPAXONE is well-controlled, results in consistency of batch-to-batch local amino acid sequences.[41] Thus, while current analytical techniques are insufficient to fully characterize the exact sequence of each polymer within the glatiramer acetate mixture, "the amino acid sequences present in glatiramer acetate are dictated by" its well-defined manufacturing process.[42]

B. Mechanism of Action of COPAXONE

By way of background, multiple sclerosis is thought to be mediated by the activation of pro-inflammatory Th1 cells in the periphery (as opposed to the central nervous system).[43] These Th1 cells cross the blood brain barrier, where they are reactivated by antigen presenting cells in the central nervous system.[44] This reactivation leads to a release of pro-inflammatory cytokines, and a cascade of events leading to destruction of the myelin sheath.[45]

Although the mechanism of action of glatiramer acetate is not fully defined, it is believed to exert its effect at least in part through the induction of a cellular immune response targeting this pathway.[46] Upon subcutaneous injection, glatiramer acetate binds to MHC class II molecules on MBP-specific antigen presenting cells.[47] This binding induces a shift from pro-inflammatory Th1 cells to anti-

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38 *Id*.

39 *Id*.

40 *Id*. at 17.

41 *Id*.; *see also* Citizen Petition Requesting that FDA Refrain from Approving any Abbreviated New Drug Application Referencing Copaxone (Glatiramer Acetate Injection) Until Certain Conditions are Met at 8 (Dec. 5, 2013); FDA Response to Teva's Citizen Petition (Docket No. FDA-2015-P-1050) at 16-17 (Apr. 16, 2015).

42 FDA Response to Teva's Citizen Petition (Docket No. FDA-2015-P-1050) at 20 (Apr. 16, 2015).

43 Wiebke Schrempf, *Glatiramer acetate: Mechanisms of action in multiple sclerosis*, 6 Autoimmunity Reviews 469, 470 (2007).

44 *Id*.

45 *Id*.

46 COPAXONE Prescribing Information at 12.

47 Caporro, *supra* note 25, at 1124; Maddalena Ruggieri, *Glatiramer Acetate in Multiple Sclerosis: A Review*, 13(2) CNS Drug Reviews 178, 180-82 (2007); Schrempf, *supra* note 43, at 470-72.

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inflammatory Th2 cells.[48] These antigen-specific Th2 cells travel across the blood brain barrier into the CNS.[49] Once in the CNS, the Th2 cells are reactivated by myelin antigens, which leads to the release of anti-inflammatory cytokines.[50] Based on this understanding, researchers have opined that unlike other multiple-sclerosis treatments, "glatiramer acetate seems to preferentially affect immune cells in an antigen-specific way."[51]

IV. COPAXONE is a "protein"

A. COPAXONE is a "chemically synthesized polypeptide"

As discussed above, any amino acid polymer that was previously defined as a "chemically synthesized polypeptide" for purposes of section 351 is necessarily a "protein," and because the exclusion for chemically synthesized polypeptides has been repealed, any such polypeptide is now a "biological product." COPAXONE previously was excluded from the definition of "biological product" because it was a chemically synthesized polypeptide. With the repeal of the exemption, COPAXONE plainly is now a "biological product." As discussed above, glatiramer acetate is a mixture of alpha amino acid polymers having an average length of 40-100 amino acids that is made entirely by chemical synthesis. Hence, COPAXONE was a "chemically synthesized polypeptide" and is now both a "protein" and a "biological product" within the meaning of section 351.

Accordingly, COPAXONE must be included on the list of products whose approved application under section 505 of the FDCA shall be deemed to be a license under section 351 of the PHSA. That it was previously excluded as a "chemically synthesized polypeptide" is enough, standing alone, to establish that it must now be included as a "protein." For completeness, however, we address in the next subsection the application of the statutory and regulatory meaning of "protein" to COPAXONE.

B. COPAXONE meets the FDA's definition of a "protein"

Even if the FDA were to disregard COPAXONE's history as a "chemically synthesized polypeptide," COPAXONE meets the FDA's definition of "protein." As discussed above, the FDA has defined "protein" for purposes of section 351 to mean "any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size."[52] Thus, to be considered a "protein" under the FDA's definition, a compound must be an alpha amino acid polymer with (1) a specific, defined sequence (2) that is greater than 40 amino acids in size.[53]

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48 *Id*.
49 *Id*.
50 *Id*.
51 Schrempf, *supra* note 43, at 470.
52 Definition of the Term "Biological Product", 83 Fed. Reg. at 63,824.
53 To be a "biological product," a "protein" must also be "applicable to the prevention, treatment, or cure of a disease or condition of human beings." PHSA § 351(i)(1), 42 U.S.C. § 262(i)(1); *see* 21

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1. COPAXONE meets the "protein" size threshold

As discussed above, the active ingredient in COPAXONE, glatiramer acetate, is a complex mixture of alpha amino acid polymers.[54] While the FDA's definition of "protein" does not directly address how the length of an amino acid polymer is calculated when the product is comprised of a plurality of distinct polymers, the proposed rulemaking provides some guidance. Specifically, the FDA explained that "for products with amino acid chains that are associated with each other in a manner that is not found in nature … FDA would conduct a fact-specific, case-by-case analysis to determine whether the size of the amino acid polymer, for purposes of this definition, should be based on adding each of the chains together, or should be based on separate consideration of the amino acid chains."[55] The FDA identified "the number of amino acids in the largest chain" as an exemplary method for determining chain length when separate consideration of multiple amino acid chains is required.[56]

The average length of the polymers in glatiramer acetate is 40-100 amino acids, which is sufficient to satisfy the length requirement under either the additive or separate chain approach.[57] The length of the largest chain is at least approximately 100 amino acids in size, so under the separate chain approach, the relevant length of glatiramer acetate is greater than 40 amino acids in size. Similarly, when all of the chain lengths of the glatiramer acetate polymers are added together, the length is of course also greater than 40 amino acids in size. Furthermore, the same conclusion is reached if one considers the average chain length of glatiramer acetate.

2. COPAXONE meets the "specific, defined sequence" requirement as applied by the Agency

The FDA's proposed definition of "protein" requires the amino acid polymer to have "a specific, defined sequence."[58] While the precise meaning of "a specific, defined sequence" is not entirely clear, the FDA's characterization of products having similar properties as "proteins" confirms that glatiramer acetate likewise meets this requirement.

First, the identity and proportion of all the amino acids that make up the individual polymers are known. Specifically, glatiramer acetate contains 14.1% glutamic acid, 42.7% alanine, 9.5% tyrosine, and 33.8% lysine on a molar basis.

Second, the specific sequence of each individual polymer – as well as the length of the individual polymers – is defined by the manufacturing process, which results in consistent amino acid sequences

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C.F.R. § 600.3(j). COPAXONE indisputably meets that prong of the definition given its approval to treat multiple sclerosis.

54 COPAXONE Prescribing Information at 12.

55 83 Fed. Reg. at 63,821.

56 *Id*.

57 Caporro, *supra* note 25, at 1124.

58 83 Fed. Reg. at 63,824.

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not only within each batch of COPAXONE, but across different batches.[59] Indeed, the FDA has found that the amino acid sequences in COPAXONE are sufficiently well-defined such that a generic product "can be shown to have the same composition and diversity of amino acid sequences."[60] More specifically, the FDA has explained that "there is a battery of characterizations that, when combined, can be applied to comparatively characterize the glatiramer acetate and provide a collection of scientific evidence sufficient to establish active ingredient sameness" such that the "FDA can conclude that generic glatiramer acetate injection has the same active ingredient as Copaxone."[61] It would make little sense to conclude that glatiramer acetate's amino acid sequence is sufficiently specific and defined that a generic product can be considered to have "the same active ingredient" as COPAXONE unless it, in fact, possesses a "specific, defined sequence." Accordingly, 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."

Teva acknowledges that the FDA has previously stated, in another context (relating to generic ANDA approval, not biological product regulation), that glatiramer acetate is distinguishable from proteins because "it does not … have a defined and specific sequence."[62] But since that time, the FDA has characterized other products with undefined and unspecified overall amino acid sequences as "proteins" within the scope of section 351. Now that the FDA is considering whether COPAXONE fits the current definition of "biological product," it should conclude that the answer is yes.

As noted above, the FDA has published a list of products previously approved under section 505 of the FDCA that now fall within the definition of "biological products" and whose approvals will be deemed to be licenses under section 351 of the PHSA as of March 23, 2020.[63] All of those products appear to be "proteins" (as opposed to some other category of "biological product"). First, the FDA issued a guidance explaining that "[t]he BPCI Act amended the definition of a 'biological product' in section 351(i) of the PHS Act to include a 'protein (except any chemically synthesized polypeptide),'" and "[t]o enhance transparency and facilitate planning for the transition date, FDA is posting on the FDA web site … a preliminary list of approved applications for biological products under the FD&C Act (as of May 31, 2018) that will be affected by the transition provision."[64] Moreover, prior to

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59 FDA Response to Citizen Petition at 20 (Apr. 16, 2015) ("the amino acid chains formed through polymerization in the synthesis of glatiramer acetate are not completely random, but rather are a reflection of the physicochemical properties of starting materials and the fundamental chemistry used to manufacture glatiramer acetate").

60 *Id*. at 21.

61 *Id*.

62 *Id*. at 12.

63 Preliminary List of Approved NDAs for Biological Products That Will Be Deemed to be BLAs on March 23, 2020 (current as of December 31, 2019), fda.gov/media/119229/download.

64 U.S. Food & Drug Admin., *The "Deemed to Be a License" Provision of the BPCI Act: Questions and Answers – Guidance for Industry* at 4-5 (Dec. 2018).

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providing this list, the FDA had explained that, "[a]lthough the majority of therapeutic biological products have been licensed under section 351 of the PHS Act, ***some protein products*** historically have been approved under section 505 of the FD&C Act (***see the Appendix to this guidance for examples of such products***)."[65] The referenced appendix included, *inter alia*, "hyaluronidase products" and "pancrelipase products," confirming that the FDA considered at least the hyaluronidase and pancrelipase products included on the list "proteins."[66]

One product included on the FDA's preliminary list of products that will be deemed to be licensed under section 351 of the PHSA is Vitrase (hyaluronidase for injection).[67] The prescribing information for Vitrase indicates that it is "a preparation of purified ovine testicular hyaluronidase, a protein enzyme."[68] However, as with glatiramer acetate, "[t]he exact chemical structure of this enzyme is unknown."[69] Vitrase's inclusion on the list of transitioning "biological products" and the FDA's identification of hyaluronidase products as "proteins" confirms that the FDA does not require that the exact overall amino acid sequence of a compound be defined or specified in order for that compound to meet the "specific, defined sequence" portion of the "protein" definition.

Another product included on the FDA's preliminary list of products that will be deemed to have a license under section 351 of the PHSA is Creon (pancrelipase).[70] Creon is a pancreatic enzyme preparation consisting of pancrelipase, an extract derived from porcine pancreatic glands.[71] Like glatiramer acetate, Creon is a complex mixture of amino acid polymers: pancrelipase comprises "multiple enzyme classes, including porcine-derived lipases, proteases, and amylases."[72] The active ingredient of Creon is thus "a very crude mixture of digestive enzymes," which are "not well

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65 U.S. Food & Drug Admin., *Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009 – Guidance for Industry* at 1 (Mar. 2016) (emphasis added).

66 *Id*. at 10.

67 Preliminary List of Approved NDAs for Biological Products That Will Be Deemed to be BLAs on March 23, 2020 (current as of December 31, 2019), fda.gov/media/119229/download.

68 Vitrase Prescribing Information at 8 (May 2018), https://www.bausch.com/Portals/77/-/m/BL/United%20States/Files/Package%20Inserts/Pharma/Vitrase-Prescribing-Info.pdf?ver=2018-07-31-131432-430.

69 *Id*.; *see also* FDA Letter Decision re: Vascepa (icosapent ethyl) Capsules (NDA 202057) Exclusivity Determination at 9 (Feb. 21, 2014) ("Although the Agency can determine whether a naturally sourced hyaluronidase product contains a member of a class of pharmacologically active enzymes (*i.e.*, of a category of hyaluronidases), the Agency cannot determine the specific enzyme or enzymes contained in any naturally sourced hyaluronidase product (*i.e.*, the structure of the precise molecule or molecules responsible for the pharmacological activity of the drug).

70 Preliminary List of Approved NDAs for Biological Products That Will Be Deemed to be BLAs on March 23, 2020 (current as of December 31, 2019), fda.gov/media/119229/download.

71 Creon Prescribing Information at 9 (Nov. 2019), https://www.rxabbvie.com/pdf/creon_PI.pdf.

72 *Id*.

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characterized or controlled."[73] As in COPAXONE, the overall sequences of the individual polymers present in Creon are unknown and differ both within each batch and from batch to batch.[74] That the FDA nevertheless identified "pancrelipase products" as "proteins" and included Creon on the list of transitioning "biological products" confirms that a mixture of polymers need not contain the same exact sequences either within or between batches to meet the "specific, defined sequence" portion of the "protein" definition.

Glatiramer acetate has an amino acid sequence that is at least as "specific" and "defined" as either of these products, and therefore should similarly meet the "specific, defined sequence" portion of the FDA's "protein" definition.

To the extent the FDA's intention in requiring a "protein" to have a "specific, defined sequence" is to instead demand the entire amino acid sequence be exactly characterized or to prohibit variability in the amino acid sequence, any such definition would be contrary to the accepted meaning of the term "protein" and unsupported by the very same scientific literature that the FDA has cited in support of its definition.[75] Furthermore, a conclusion that glatiramer acetate does not have a "specific, defined sequence" either because the precise sequence of its polypeptides is not known or because it does not exhibit the exact same polypeptide amino acid sequences in every batch would be arbitrary and capricious given the FDA's contrary treatment of hyaluronidase and pancrelipase products.[76]

For the foregoing reasons, COPAXONE falls within the definition of a "protein" as that term has been interpreted by the FDA—including the aspects of the agency's definition that are not in the statute. It follows that COPAXONE meets the statutory definition as well. Accordingly, COPAXONE should be considered a "biological product" and included on the list of applications that will be deemed to be a license under section 351 of the PHSA as of March 23, 2020.

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[73] Center for Drug Evaluation and Research, Application No. 20-725, Chemistry Review(s), 8 (Mar. 2009), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/020725s000ChemR.pdf.

[74] FDA Letter Decision re: Vascepa (icosapent ethyl) Capsules (NDA 202057) Exclusivity Determination at 9 (Feb. 21, 2014) ("no sponsor has identified a particular lipase, amylase, or protease that is present consistently or active in every lot of any particular pancrelipase mixture, nor has any pancrelipase mixture been characterized adequately to allow the Agency to identify which molecule or molecules in a particular pancrelipase product, among the possibly hundreds of different enzyme variants present, is responsible for that pancrelipase's physiological or pharmacological action.")

[75] *See* 83 Fed. Reg. at 63,819.

[76] *E.g., Encino Motorcars, LLC v. Navarro*, 136 S. Ct. 2117, 2126 (2016) ("[U]nexplained inconsistency is a reason for holding an interpretation to be an arbitrary and capricious change from agency practice") (citation omitted).

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V. At a minimum, COPAXONE is an "analogous product"

Even if COPAXONE were not within any of the express categories in the definition of "biological product," it would still be a "biological product" because, at a minimum, it fits squarely into the catchall category of "an analogous product."

The "biological products" regulated under section 351 of the PHSA have always included not only the expressly enumerated categories (*e.g.*, virus, therapeutic serum, or toxin), but also "an analogous product."[77] As originally enacted, the predecessor statute embraced "any virus, therapeutic serum, toxin, antitoxin, or analogous product."[78] When Congress first amended the statute to include additional categories (*i.e.*, vaccine, blood, blood component or derivative, and allergenic product), they were inserted ***between*** "antitoxin" and "analogous product," thus broadening "analogous product" to refer back to the newly added categories as well as the old.[79]

With the passage of the BPCIA, "protein (except any chemically synthesized polypeptide)" was added to the definition of "biological product"—again, between the existing previous categories and "analogous product"—effectively expanding the scope of "analogous products" to include products analogous to proteins.[80] Of course, the general "analogous product" catchall could not have been used to circumvent the express exclusion of "chemically synthesized polypeptides" from the definition. Now that this exclusion has been removed by the 2020 Act, however, the scope of "analogous product" has been broadened yet again, this time to include all products analogous to any "proteins," including those that are chemically synthesized. To the extent COPAXONE is not a "protein" within the meaning of section 351 of the PHSA, it should nevertheless be considered a "biological product" because it is an "analogous product" within the meaning of the statute.

While the FDA has not updated its definitions of the term "analogous product" to reflect the 1970, 2010, or 2020 changes to the definition of "biological product,"[81] those regulations suggest that a product should certainly qualify as "analogous," and thus as a biological product, when it is derived from the same building blocks as a protein, falls into the length range attributed to proteins,[82] and is used to affect the immune system for therapeutic purposes in a manner comparable to other biological

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77 *See, e.g.*, Food and Drug Administration Modernization Act of 1997, § 123(d), 111 Stat. at 2324 (initial definition of "biological product").

78 Act of July 1, 1902, ch. 1378, 32 Stat. 728.

79 Act of Oct. 30, 1970, Pub. L. No. 91-515, § 291, 84 Stat. 1297, 1308.

80 BPCIA § 7002(b), 124 Stat. at 814.

81 *See* 21 C.F.R. § 600.3(h)(5)(i)-(iii) (addressing "analogous products" only with reference to the original categories of virus, therapeutic serum, toxin, and antitoxin).

82 *Cf., e.g.*, *id.* § 600.3(h)(5)(i)-(ii) (products defined as analogous based on their common origin, preparation, or derivation, such as a product "derived from whole blood").

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products.[83] That is consistent with the legislative history, which explained at the time Congress added the term "vaccine"—"a general term which covers products intended to stimulate antibodies to specific diseases"—that the inclusion of such products was "consistent with the intent of the original [statute as enacted in] 1902."[84]

The functional meaning of "analogous product" is supported by the United States Department of Agriculture's ("USDA's") interpretation of the same term in closely related context. The Virus-Serum-Toxin Act ("VSTA") authorizes the USDA to regulate biological products intended for use in the treatment of domestic animals.[85] The types of products regulated under the VSTA include a "virus, serum, toxin, or analogous product."[86] The USDA's implementing regulations define "analogous product" to include, inter alia, "[s]ubstances, at any stage of production, shipment, distribution, or sale, which are intended for use in the treatment of animals *and which are similar in function to biological products in that they act, or are intended to act, through the stimulation, supplementation, enhancement, or modulation of the immune system or immune response*."[87] As noted, that is consistent with the FDA's longstanding interpretation that a product is "analogous … to 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."[88] That is true not just of toxins and antitoxins: as the Fifth Circuit noted in construing the term "analogous product" before the 1970 amendments, *all* "[t]he products enumerated in the 1902 statute are immunological agents."[89] Thus, any product that is "similar in function to biological products" or acts "through the stimulation, supplementation, enhancement or modulation of the immune system or immune response" is an "analogous product" and therefore a "biological product" within the meaning of section 351 of the PHSA.

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83 *Cf., e.g.*, *id.* § 600.3(h)(5)(iii) (products defined as analogous "irrespective of [their] source of origin" if intended "to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process").

84 H.R. Rep. No. 91-1035, at 3 (1970) (House report on predecessor bill H.R. 15961); *id.* at 6 (identical definition in transmittal letter from HEW Secretary Robert H. Finch); *see also* H.R. Rep. No. 91-1590, at 22 (1970) ("This amendment is identical to the provision of H.R. 15961, already passed by the House.").

85 Act of Mar. 4, 1913, ch. 145, § 1, 37 Stat. 828, 832-33 (codified as amended at 21 U.S.C. §§ 151-159).

86 *E.g.*, 21 U.S.C. § 151.

87 9 C.F.R. § 101.2 (emphasis added) (subparagraph (2) of definition of "biological products").

88 21 C.F.R. § 600.3(h)(5)(iii).

89 *Blank v. United States*, 400 F.2d 302, 304 (5th Cir. 1968). While the Agency's predecessor disagreed with *Blank*'s specific holding, and Congress expanded the definition of "biological product" in response to *Blank* (ensuring that blood products would be included), the amendments did not make "analogous product" any *less* broad.

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Glatiramer acetate is a synthetic analog of myelin basic protein, or MBP, and exhibits both structural and functional similarities to that naturally occurring protein.[90] The scientific literature consistently refers to MBP as a "protein."[91] As a "protein," MBP is incontrovertibly a "biological product."[92] Like glatiramer acetate, MBP is a complex, heterogenous mixture of polypeptides, which together define its structure and function.[93] The structural similarities between glatiramer acetate and MBP do not stop there; many of the polypeptide sequences of glatiramer acetate align with those of MBP.[94] In fact glatiramer acetate polypeptides have been found to "mimic[] the least-folded regions of MBP."[95] Thus, glatiramer acetate is structurally comparable to MBP. Glatiramer acetate is also similar in function to, and in fact, "has been suggested to mimic certain properties of MBP."[96] Glatiramer acetate competes with MBP to bind with MHC class II molecules on MBP-specific antigen presenting cells, thus indicating the functional similarity of these compounds.[97]

Beyond the specific example of MBP, glatiramer acetate is also both functionally and structurally similar to biological products generally. First, glatiramer acetate modulates an immune response – *i.e.*, a shift in T helper cells from Th1 to Th2 – a function typically associated with biological products.[98] In fact, the FDA has acknowledged the potential immunogenicity concern associated with generic glatiramer acetate products.[99] For those reasons, numerous researchers have described COPAXONE as a "vaccine."[100] Even the FDA reviewer of COPAXONE expressed the view that

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90 Romualdas Stapulionis, *Structural Insight into the Function of Myelin Basic Protein as a Ligand for Integrin αMβ2*, 180 *Journal of Immunology* 3946, 3946 (2008); Caporro, *supra* note 25, at 1124.

91 See, *e.g.*, George Harauz, *Myelin Management by the 18.5-kDa and 21.5-kDa Classic Myelin Basic Protein Isoforms*, 125 J. Neurochem. 334, 334-61 (2013); Stapulionis, *supra* note 90, at 3946.

92 PHSA § 351(i)(1), 42 U.S.C. § 262(i)(1).

93 Harauz, *supra* note 91, at 335.

94 Stapulionis, *supra* note 90, at 3950.

95 *Id*. at 3954.

96 *Id*. at 3950.

97 Caporro, *supra* note 25, at 1124.

98 Schrempf, *supra* note 43, at 471; see also Liang Zhao, *Clinical pharmacology considerations in biologics development*, 33 Acta Pharmacologica Sinica 1339, 1344 (2012) (defining "biological products" to include products that "act primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response")

99 FDA Response to Citizen Petition at 39 (Apr. 16, 2015) ("As discussed elsewhere in this response, Copaxone has an array of peptide copolymers that can activate the immune system and stimulate an immune response. We agree that a generic glatiramer acetate injection must not elicit a different immune response from Copaxone."); *see also* Zhao, *supra* note 98, at 1344 ("Another distinction between small molecules and biologics is that biologics can be immunogenic.")

100 *See*, *e.g.*, *id*. ("GA is one of the few practical examples of therapeutic vaccination"); Tjalf Ziemssen, *Glatiramer Acetate: Mechanisms of Action in Multiple Sclerosis*, 79 International Review of Neurobiology, 537, 552 (2007) ("GA is one of the few positive examples of an antigen-based, therapeutic vaccination"); Michael Sela, *Immunomodulatory Vaccines Against Autoimmune Diseases*, 9 Rejuvenation Res. 126, 127 (2006) ("At least one therapeutic vaccine (copolymer 1 or glatiramer acetate

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COPAXONE's "mechanism of action is most likely as a ***vaccine*** that induces an immune response that interferes with the ongoing autoantigenic immune response against myelin basic protein thought to be the cause for the symptomology associated with multiple sclerosis (MS)."[101] That mechanism of action alone confirms that COPAXONE is functionally "analogous" to other biological products, including but not limited to both proteins and vaccines.[102]

Second, glatiramer acetate is absorbed through the lymphatic system, "the major route of absorption for biologics."[103] Third, glatiramer acetate's molecular weight of 5,000-9,000 daltons is far greater than the typical small-molecule drug and on the order of those commonly associated with biological products.[104]

Because glatiramer acetate is analogous to a "biological product" both structurally and functionally, COPAXONE is an "analogous product" in every relevant sense. For this reason, too, COPAXONE should be considered a "biological product" and included on the list of applications that will be deemed to be a license under section 351 of the PHSA as of March 23, 2020.

[GA]) for the relapsing-remitting form of multiple sclerosis (MS), is being used by many tens of thousands of patients.")

[101] Review and Evaluation of Pharmacology Toxicology Data, Original NDA Review (NDA No. 20-622) at 126 (emphasis added).

[102] Even products that are not analogous to a *protein* can be analogous to other biological products, such as vaccines. *See* 83 Fed. Reg. at 63,822 ("[V]accines are specifically identified as biological products under the statutory definition in section 351(i) of the PHS Act irrespective of their size, content, or method of manufacture.").

[103] Zhao, *supra* note 98, at 1340; see also COPAXONE Prescribing Information at 12 ("Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some may enter the systemic circulation intact").

[104] Zhao, *supra* note 98, at 1340 ("The molecular weight of a small molecule drug is typically less than 1 kDa (20–100 atoms), whereas the molecular weights of biologics range from a few kDa to 1000 kDa.").

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VI. Conclusion

In view of the above, Teva respectfully submits that COPAXONE is a "biological product," and therefore subject to regulation under section 351 of the PHSA. Accordingly, under section 7002(e)(4) of the BPCIA, the approved NDA for COPAXONE must be "deemed to be a license" under section 351 on March 23, 2020.

Teva appreciates the opportunity to submit comments on this important topic and respectfully requests that the Agency add COPAXONE to the list of products that will transition to BLAs on March 23, 2020. If the Agency would like to discuss any aspect of our submission, please do not hesitate to contact me.

Sincerely,

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